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# AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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PHILADELPHIA AND NEW YORK
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# AMERICAN JOURNAL

# OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### A CLINICAL STUDY OF A THOUSAND CASES OF ULCER OF THE STOMACH AND DUODENUM.[1]

By Julius Friedenwald, M.D.,

PROFESSOR OF GASTRO-ENTEROLOGY IN THE COLLEGE OF PHYSICIANS AND SURGEONS, BALTIMORE

In the study of the thousand cases of ulcer of the stomach and duodenum, great care has been exercised to eliminate all cases in which there has been the slightest question as to the diagnosis, and suspected cases in which the diagnosis has been the least doubtful have been excluded from this report. The thousand cases occurred in 12,598 patients effected with various gastric disturbances (7.8 per cent.).

Age. As is observed in the following table, the largest proportion of cases occur between the twentieth and fiftieth years and the greatest number between the twentieth and thirtieth years:

| Age. | Cases. | Per cent. |
|---|---|---|
| 0 to 10 | 2 | 0.20 |
| 10 to 20 | 162 | 16.20 |
| 20 to 30 | 345 | 34.50 |
| 30 to 40 | 229 | 22.90 |
| 40 to 50 | 128 | 12.50 |
| 50 to 60 | 93 | 9.30 |
| 60 to 70 | 38 | 3.80 |
| Over 70 | 3 | 0.30 |

Sex. Of the total number of cases there are 676 males and 324 females. The following table illustrates the number of cases observed in males and females according to age:

[1] Presented at the Meeting of the Association of American Physicians, held at Atlantic City, May 14, 1912.

| Years. | Males. | Females. | Total. |
|---|---|---|---|
| 0 to 10 | 2 | 0 | 2 |
| 10 to 20 | 124 | 38 | 162 |
| 20 to 30 | 262 | 83 | 345 |
| 30 to 40 | 119 | 110 | 229 |
| 40 to 50 | 91 | 37 | 128 |
| 50 to 60 | 48 | 45 | 93 |
| 60 to 70 | 29 | 9 | 38 |
| Over 70 | 1 | 2 | 3 |

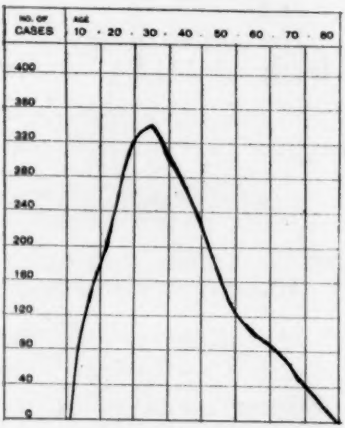


FIG. 1.—Age diagram of 1000 cases of ulcer.

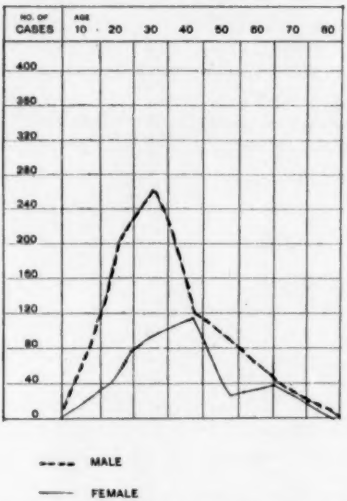


FIG. 2.—Sex and age diagram of 1000 cases of ulcer.

Of the 1000 cases, 31 were found in cooks, 18 in workers in metals, 12 in workers in porcelain, 8 were miners, 28 were tailors, 15 were shoe makers, and 19 were blacksmiths.

A definite history of trauma was elicited in 23 cases, in 10 of which there had been blows on the abdomen.

ANEMIA. In 324 of our cases in which hemoglobin estimations had been recorded, anemia was present in 211 cases (65 per cent.). The average of the hemoglobin estimations was 61 per cent.; this does not, however, include those cases accompanied by severe hemorrhages. In 302 cases in which hematemesis or melena occurred, the average hemoglobin estimation was 46 per cent.

CARDIAC AND VASCULAR CHANGES. Chronic endocarditis was present in 43 cases (4.3 per cent.); arteriosclerosis in 153 (15.3 per cent.).

PREVIOUS DISORDERS OF DIGESTION. In the 1000 cases there was a history of some previous digestive distrubance in 482 cases (48.2 per cent.). Some of these disturbances must have been premonitory symptoms of the ulcer itself, inasmuch as there is often great difficulty in distinguishing early signs of ulcer from ordinary slight gastric disturbances.

EXCESSES IN FOOD AND DRINK. The history of former indiscretions in diet was obtained in 433 instances (43.3 per cent.); but only in 129 (12.9 per cent.) did the patient attribute his disease to some specific error in diet.

A history of alcoholism was obtained in 214 instances (21.4 per cent.).

INFECTIOUS DISEASES. A history of syphilis was obtained in 52 instances, yet only in 5 could the ulcer be directly attributed to this disease. Tuberculosis of the lungs was present in 26 instances, but as far as could be observed this disease appeared to have no etiological bearing upon the production of the ulcer.

THE GASTRIC SECRETION IN ULCER. Of the thousand cases the gastric secretion was examined in 810 instances.

| | Cases. | Per cent. |
|---|---|---|
| Normal acidity was observed in | 376 | 46.4 |
| Hyperchlorhydria was observed in | 246 | 30.3 |
| Hypochlorhydria and anacidity | 188 | 23.2 |
| | 810 | |

Of the 810 cases, consisting of 516 males and 294 females, the acidities were as follows:

| | Males. | | Females. | |
|---|---|---|---|---|
| | Cases. | Per cent. | Cases. | Per cent. |
| Normal acidity | 271 | 33.5 | 105 | 12.9 |
| Hyperchlorhydria | 161 | 19.8 | 85 | 10.5 |
| Hypochlorhydria and anacidity | 84 | 10.4 | 104 | 12.8 |
| | 516 | | 294 | |

Hyperacidity was proportionately more frequently observed in males and subacidity in females, while the greatest number of males as well as females presented a normal acidity. It is interesting to note the relation of acidities to the duration of the disease. In acute ulcers and especially those accompanied by recent hemorrhages, the acidity is very high, while in chronic forms the acidity is low. In 128 cases of acute ulcer of which 75 were males and 53 were females, 96 (61 males and 35 females), presented high acidities.

| | Males. | | Females. | |
|---|---|---|---|---|
| | Cases. | Per cent. | Cases. | Per cent. |
| Normal acidity | 12 | 9.3 | 8 | 0.6 |
| Hyperchlorhydria | 61 | 47.6 | 35 | 27.3 |
| Hypochlorhydria | 2 | 1.6 | 10 | 7.7 |
| | 75 | | 53 | |

Of the 426 cases of chronic ulcers of long duration the tendency is toward low acidities. The following table illustrates this condition:

| | Males. | | Females. | |
|---|---|---|---|---|
| | Cases. | Per cent. | Cases. | Per cent. |
| Normal acidity | 94 | 22.0 | 85 | 19.9 |
| Hyperchlorhydria | 35 | 8.3 | 39 | 9.1 |
| Hypochlorhydria | 80 | 18.6 | 93 | 21.8 |
| Total | 209 | 48.9 | 217 | 50.8 |

DURATION OF SYMPTOMS. The average duration of symptoms in ulcer is twelve years. The following table illustrates the average duration of symptoms in males and females according to age:

| Age. | Males. | Average duration of symptoms in years. | Females. | Average duration of symptoms in years. |
|---|---|---|---|---|
| 0 to 10 | 2 | ½ | 0 | |
| 10 to 20 | 124 | 2 | 38 | 1½ |
| 20 to 30 | 262 | 11 | 83 | 10½ |
| 30 to 40 | 119 | 19 | 110 | 13½ |
| 40 to 50 | 91 | 14 | 37 | 16 |
| 50 to 60 | 48 | 16½ | 45 | 19 |
| 60 to 70 | 29 | 17 | 9 | 19½ |
| Over 70 | 1 | 20 | 2 | 12 |

PAIN. Pain, the most prominent feature of ulcer was present in 94 per cent. of our cases. It is most prominent in those cases accompanied by hyperchlorhydria. Of the 810 cases in which the gastric contents was analyzed the relation of pain to acidity is presented in the following table, from which it is evident that pain is most pronounced in those instances associated with high acidity:

| | | Absent. | | | Moderate. | | Moderately severe. | | Severe. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cases. | No. | % | No. | % | No. | % | No. | % |
| Normal acidity | 376 | 2 | 0.2 | 92 | 11.3 | 123 | 15.1 | 159 | 19.6 |
| Hyperchlorhydria | 246 | 1 | 0.1 | 8 | 9.0 | 35 | 4.3 | 202 | 24.9 |
| Hypochlorhydria | 188 | 7 | 0.7 | 59 | 7.3 | 82 | 10.1 | 40 | 5.0 |

TIME OF APPEARANCE OF PAIN. Of the 1000 cases the pain appeared within the first hour after meals in 223 instances, between one and two hours in 188, after two hours in 491, and in 38 it appeared irregularly.

EFFECT OF FOOD UPON PAIN. The pain was aggravated in 212 instances by the ingestion of food and was relieved in 619 instances by the taking of food. In 109 instances the pain was neither increased nor relieved by the taking of food.

INTERMISSIONS OF PAIN. In 563 instances of the 940 cases in which pain was present, there were one or more periods in which distinct intermissions of pain occurred varying from one to twelve months or more. The following table presents these according to periods of intermission in months:

| Cases. | Months of intermission. |
|---|---|
| 94 | 1 to 2 |
| 72 | 2 to 3 |
| 82 | 3 to 4 |
| 79 | 4 to 5 |
| 48 | 5 to 6 |
| 26 | 6 to 7 |
| 38 | 7 to 8 |
| 34 | 8 to 9 |
| 17 | 9 to 10 |
| 20 | 10 to 11 |
| 31 | 11 to 12 |
| 22 | 12 or more. |
| 563 | |

TENDERNESS. Of the 1000 cases epigastric tenderness was present in 908 cases (90.8 per cent.). A tender area was noted to the right of the median line in 41 cases (4.1 per cent.). The dorsal together with an epigastric tender spot, was noted in 523 instances (52.3 per cent.). A dorsal area alone in 25 (2.5 per cent.). No tender area in 26 instances (2.6 per cent.).

VOMITING. Vomiting is another very prominent symptom, though not as constant as the pain. It occurred in 676 of our cases (67.6 per cent.). It is proportionately more frequent in those instances in which pain appears early. Of the 940 cases in which pain was present there were 223 having pain within the first hour, of which 194 had vomiting. There were 188 with pain between the first and second hours, of which 143 had vomiting; 529 manifested pain two hours after meals, (or pain appeared irregularly), of which 324 had vomiting. The following table illustrates this condition:

| Time of appearance of pain in hours. | Cases with pain. | Cases with vomiting. | General per cent. | Per cent. of cases of vomiting in proportion to the cases with pain. |
|---|---|---|---|---|
| In one hour | 223 | 194 | 29.3 | 87.0 |
| In one to two hours | 188 | 143 | 21.6 | 76.6 |
| After two hours or irregularly | 529 | 324 | 49.0 | 61.2 |
| Total | 940 | 661 | | |

Of the 40 cases of ulcer not accompanied by pain, vomiting occurred in 16 cases (40 per cent.).

VOMITING AND ACIDITY. Of the 810 cases in which an examination was made of the gastric contents, the relation of the vomiting to the acidity is illustrated in the accompanying table. There were 676 of these cases in which vomiting was present. Of these there were 531 in which analyses were made. Vomiting is definitely more prominent in those instances accompanied by high acidity.

| Acidity. | Cases. | Moderate vomiting. | | Severe vomiting. | |
|---|---|---|---|---|---|
| | | Number. | Per cent. | Number. | Per cent. |
| Normal acidity | 298 | 125 | 23.5 | 171 | 32.5 |
| Hyperchlorhydria | 138 | 18 | 3.3 | 122 | 22.8 |
| Hypochlorhydria | 95 | 76 | 14.3 | 19 | 3.5 |

HEMATEMESIS. Gastric hemorrhage was manifested or a history of this symptom was presented in 228 of the 1000 cases, that is in 22.8 per cent. In the following table the proportion of cases accompanied by a single hemorrhage or with multiple hemorrhages are presented according to age:

| Years. | Cases with hemorrhage. | Per cent. of cases with hemorrhage. | Proportion cases single hemorrhage. | | Proportion cases multiple hemorrhage. | |
|---|---|---|---|---|---|---|
| | | | Number. | Per cent. | Number. | Per cent. |
| 0 to 10 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| 10 to 20 | 48 | 21.0 | 17 | 7.4 | 31 | 13.6 |
| 20 to 30 | 81 | 35.5 | 23 | 10.0 | 58 | 25.4 |
| 30 to 40 | 42 | 18.3 | 28 | 12.7 | 13 | 5.7 |
| 40 to 50 | 29 | 12.8 | 8 | 3.4 | 21 | 9.0 |
| 50 to 60 | 20 | 8.8 | 6 | 2.6 | 14 | 6.0 |
| 60 to 70 | 8 | 3.5 | 6 | 2.6 | 2 | 0.9 |
| Over 70 | 0 | 0.0 | 0 | 0.0 | 0 | .0 |
| Total | 228 | 99.6 | 89 | 38.7 | 139 | 60.6 |

MELENA. Tar-colored stools or a history of this condition was presented in 515 of the 1000 cases, that is 51.5 per cent. The following table illustrates the number and percentage of these cases at various ages; the largest proportion appearing between the tenth and thirtieth years:

| Years. | Cases with melena. | Per cent. of cases with melena. |
|---|---|---|
| 0 to 10 | 0 | 0.0 |
| 10 to 20 | 103 | 10.3 |
| 20 to 30 | 161 | 16.1 |
| 30 to 40 | 98 | 9.8 |
| 40 to 50 | 66 | 6.6 |
| 50 to 60 | 61 | 6.1 |
| 60 to 70 | 24 | 2.4 |
| Over 70 | 2 | 0.2 |
| Total | 515 | 51.5 |

It is also interesting to note the proportion of cases with melena, and to compare this condition with hematemesis observed at various

ages, as is illustrated in the accompanying table. Melena is over twice as frequent as gastric hemorrhage and occurs much more frequently after the fortieth year of age than is observed with hematemesis.

COMPARISON OF CASES WITH HEMATEMESIS AND MELENA AT VARIOUS AGES.

| Ages. | Gastric hemorrhage. | | Melena. | |
|---|---|---|---|---|
| | Cases. | Per cent. | Cases. | Per cent. |
| 0 to 10 | 0 | 0.0 | 0 | 0.0 |
| 10 to 20 | 48 | 4.8 | 103 | 10.3 |
| 20 to 30 | 81 | 8.1 | 161 | 16.1 |
| 30 to 40 | 42 | 4.2 | 98 | 9.8 |
| 40 to 50 | 29 | 2.9 | 66 | 6.6 |
| 50 to 60 | 20 | 2.0 | 61 | 6.1 |
| 60 to 70 | 8 | 0.8 | 24 | 2.4 |
| Over 70 | 0 | 0.0 | 2 | 0.2 |
| | 228 | | 515 | |

There were 287 cases accompanied by melena without any evidence of hematemesis. These cases are presented according to age in the following table. They are cases of duodenal ulcers which are to be presented later on.

| Age. | Cases. | Per cent. |
|---|---|---|
| 10 to 20 | 55 | 19.5 |
| 20 to 30 | 82 | 28.3 |
| 30 to 40 | 56 | 19.5 |
| 40 to 50 | 37 | 12.9 |
| 50 to 60 | 41 | 14.2 |
| 60 to 70 | 16 | 5.5 |
| Over 70 | 0 | 0.0 |
| Total | 287 | |

OCCULT BLOOD. The test for occult blood was made constantly only with feces. The stools were examined in 539 cases of the 1000 cases. Of these 467 gave one or more positive results (86.6 per cent.). The examinations here noted were only made in those instances in which visible blood was absent, or had not appeared for a considerable length of time before the test had been made. Blood was not always present in the first test but frequently appeared sometime during the course of the disorder.

EINHORN STRING TEST. The string test was made in 41 of our cases and was found positive in 34 (83 per cent.). The results obtained by means of this test are about as sensitive as the test for occult blood.

COMPLICATIONS. Atony of the stomach was noted in 321 (32.1 per cent.) of our cases and enteroptosis was noted in 411 instances (41.1 per cent.). Evidences of dilatation of the stomach were observed in 336 instances (38.4 per cent.). A tumor was palpable in the form of an hypertrophied pylorus in 25 of our cases (2.5 per cent.), and perforation occurred in 10 cases (1 per cent.).

DUODENAL ULCERS. Of the 1000 cases of ulcer 529 were duodenal (52.9 per cent.), and 409 gastric (40.9 per cent.), and 62 (6.2 per cent.) undetermined. The largest number of duodenal ulcers occurred between the twentieth and thirtieth years. The following table illustrates the number of cases of duodeanl ulcer arranged according to age:

| Years. | Cases. | Per cent. |
|---|---|---|
| 10 to 20 | 55 | 10.3 |
| 20 to 30 | 159 | 30.0 |
| 30 to 40 | 149 | 28.2 |
| 40 to 50 | 91 | 17.2 |
| 50 to 60 | 43 | 8.2 |
| 60 to 70 | 32 | 6.0 |
| Over 70 | 0 | 0.0 |
| | 529 | |

SEX. The largest proportion of cases occurred in males, *i. e.*, 307 males (58 per cent.), and 222 females (42 per cent.). The following table indicates the number of males and females at various ages:

| | Males. | | Females. | |
|---|---|---|---|---|
| Years. | No. | Per cent. | No. | Per cent. |
| 10 to 20 | 31 | 5.8 | 24 | 4.5 |
| 20 to 30 | 85 | 16.1 | 74 | 13.9 |
| 30 to 40 | 87 | 16.4 | 62 | 11.7 |
| 40 to 50 | 66 | 12.4 | 25 | 4.7 |
| 50 to 60 | 11 | 2.0 | 32 | 6.0 |
| 60 to 70 | 27 | 5.1 | 5 | 0.9 |
| | 307 | | 222 | |

ACIDITY. Of the 529 cases the secretion was analyzed in 402. Of the 402 there were 195 with normal acidity, 142 with hyperchlorhydria, and 65 with hypochlorhydria. The accompanying table illustrates this condition:

| | No. | Per cent. |
|---|---|---|
| Normal acidity | 195 | 48.5 |
| Hyperchlorhydria | 142 | 35.3 |
| Hypochlorhydria | 65 | 16.1 |
| | 402 | |

Of the 402 cases there were 213 males and 189 females which are arranged according to their acidities in the following table. Hyperacidity being more frequently observed in males and subacidity in females.

| | Male. | | Female. | | Total. | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| Normal acidity | 120 | 29.7 | 75 | 18.6 | 195 | 48.3 |
| Hyperchlorhydria | 79 | 19.6 | 63 | 15.6 | 142 | 35.2 |
| Hypochlorhydria | 14 | 3.4 | 51 | 12.4 | 65 | 18.8 |

PAIN. Pain was present in 512 of our duodenal cases (96.5 per cent.). It was absent in 17 cases. It was most prominent in those cases with hyperacidity. Of the 402 cases in which the gastric contents were examined, the relation of the pain to the acidity is illustrated in the following table; the pain being more severe in those instances associated with high acidity:

| | | Absent. | | Mild. | | Moderately severe. | | Severe. | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases. | No. | Per cent. | No. | Per cent. | No. | Per cent. | No. | Per cent. |
| Normal acidity | 195 | 1 | 0.2 | 45 | 12.1 | 59 | 14.6 | 90 | 22.1 |
| Hyperchlorhydria | 142 | 1 | 0.2 | 6 | 1.4 | 24 | 5.9 | 111 | 27.3 |
| Hypochlorhydria | 65 | 5 | 1.2 | 25 | 6.2 | 10 | 2.4 | 25 | 6.2 |

INTERMISSIONS OF PAIN. Of the 512 cases in which pain was present, 316 presented records showing distinct periods in which the pain had disappeared for a time; one month to twelve months or more (63 per cent.). The following table illustrates the number of cases presenting the intermissions of pain according to the number of months.

| Cases. | Intermissions in pain in months. |
|---|---|
| 53 | 1 to 2 |
| 36 | 2 to 3 |
| 44 | 3 to 4 |
| 37 | 4 to 5 |
| 34 | 5 to 6 |
| 17 | 6 to 7 |
| 23 | 7 to 8 |
| 29 | 8 to 9 |
| 9 | 9 to 10 |
| 15 | 10 to 11 |
| 14 | 11 to 12 |
| 5 | 12 or more. |

TENDERNESS. Of the 529 cases epigastric tenderness was present in 474 cases (89.4 per cent.). A tender area to the right or left of the median line in 41 cases (7.7 per cent.). A dorsal tender area together with an epigastric spot was present in 289 cases (54.6 per cent.), and a dorsal tender area alone in 6 cases (1.1 per cent.), no tender area in 8 cases (1.5 per cent.).

VOMITING. Vomiting occurred in 113 of our duodenal ulcers, that is 21 per cent.

VOMITING AND ACIDITY. Of the 402 cases in which the gastric contents was analyzed the relation of the acidity to vomiting is as illustrated in the fololwing table. There were 113 cases in which vomiting occurred, of which the gastric contents was examined in 92. It is here demonstrated that vomiting is more frequent in those cases accompanied by high acidity.

| | No. | Moderate vomiting. | | Severe vomiting. | |
|---|---|---|---|---|---|
| Normal acidity | 48 | 20 | 4.8 | 28 | 30.4 |
| Hyperchlorhydria | 38 | 6 | 6.5 | 32 | 34.8 |
| Hypochlorhydria | 6 | 5 | 5.4 | 1 | 1.0 |

MELENA. Tar-colored stools or a history of this condition appeared in 287 of our 529 cases, (54 per cent.). The following table presents the number of cases according to age.

| Age. | Cases. | Per cent. |
|---|---|---|
| 10 to 20 | 55 | 19.5 |
| 20 to 30 | 82 | 28.3 |
| 30 to 40 | 56 | 19.5 |
| 40 to 50 | 37 | 12.9 |
| 50 to 60 | 41 | 14.2 |
| 60 to 70 | 16 | 5.5 |

OCCULT BLOOD. Of the 529 cases, an examination of the feces was made in 381. Of this number, 315 presented one or more positive tests for occult blood (83 per cent.). The examinations here noted include those cases alone in which visible blood was entirely absent, or had not been present for a considerable length of time before the test for occult blood was made. The blood was frequently absent in the first examination but usually appeared sometime during the course of the disorder, and especially when the symptoms became aggravated. It gradually disappeared as recovery took place.

RESULTS OF TREATMENT OF GASTRIC AND DUODENAL ULCERS. Of the 1000 cases, 885 were under direct observation during the entire course of treatment. In the remaining 115, the diagnosis was simply made, treatment was not instituted, or if so, was only imperfectly carried out.

Of the 885 cases, 794 were treated medically and 91 surgically. Of the 794 treated medically, 20 were required to seek surgical aid later on account of the failure of medical treatment. Of the 794 treated medically, 521 undertook the rest cure treatment, while 273 were treated as ambulatory patients.

Of the 521 treated by the rest cure, 404 had the Leube treatment, and 117 the Lenhartz treatment, or a slight modification of the same. Of the 404 treated by the Leube, 291 or 72 per cent. were cured, 97 or 24 per cent. were not cured, and 16 or 4 per cent. died. Of the 117 treated by the Lenhartz treatment, 78 or 66 per cent. were cured, 34 or 29 per cent. were not cured, and 5 or 5 per cent. died.

Of the 273 cases treated as ambulatory patients, 153 were treated with nitrate of silver, 110 with subnitrate of bismuth, and 10 by the olive oil method. Of the 153 treated with the nitrate of silver, 73 or 47 per cent. were cured, while 80 or 53 per cent. were not cured. Of the 110 treated with subnitrate of bismuth, 56 or 50 per cent. were cured, while 54 or 49 per cent. were not cured. Of the 10 treated by the olive oil method, 4 or 40 per cent. were cured, while 6 or 60 per cent. were not cured. The following table illustrates the percentage of recovery by various methods of treatment:

| No. | Form of treatment. | Cured. No. | Cured. Per cent. | Not cured. No. | Not cured. Per cent. | Died. No. | Died. Per cent. |
|---|---|---|---|---|---|---|---|
| 404 | Leube . . . . . | 291 | 72 | 97 | 24 | 16 | 4 |
| 117 | Lenhartz . . . . . | 78 | 66 | 34 | 29 | 5 | 5 |
| 153 | Nitrate of silver . . | 73 | 47 | 80 | 53 | Ambulatory cases. | |
| 110 | Subnitrate of bismuth . | 56 | 50 | 54 | 49 | Ambulatory cases. | |
| 10 | Olive oil . . . . . | 4 | 40 | 6 | 60 | Ambulatory cases. | |

End Results. Of the 291 cases treated by the Leube method and cured, 83 could be followed for a period of five years or longer after the treatment. Of these, 62 or 74 per cent. remained permanently well, and 21 or 25 per cent. had relapses.

Of the 78 treated by the Lenhartz treatment, and cured, 45 could be followed for a period of five years or longer after the treatment. Of these, 35 or 77 per cent. remained permanently well, while 10 or 22 per cent. had relapses.

Results of Surgical Treatment. Of the 91 cases operated on, 64 or 71 per cent. were cured, 20 or 22 per cent. were not cured, and 7 or 70 per cent. died. Of these 10 had perforations, of which 6 or 60 per cent. recovered, while 4 or 40 per cent. died.

End Results. Of the 64 cases operated on, and cured, 45 could be followed for a period of five years or longer, after treatment. Of these, 41 or 91 per cent. remained permanently well, and 4, or 9 per cent. had relapses.

Einhorn Duodenal Feeding. A few cases of ulcer which did not yield to the usual treatment were treated by Einhorn's duodenal method of feeding. While the results seemed satisfactory, the number of cases was too few to be incorporated in this report.

Conclusions. From a careful study of the 1000 cases of ulcers of the stomach and duodenum, the following conclusions may be safely drawn.

1. In patients suffering from various gastric disturbances, 7.8 per cent. are affected with ulcers.

2. The largest proportion of ulcers occur between the twentieth and fiftieth year of age.

3. More than twice as many males are affected as females.

4. Anemia is present in a large proportion of the cases of ulcer.

5. A history of over-indulgence in food or drink can be obtained in almost half of the number of cases of ulcer.

6. The greatest proportion of cases of ulcer presents a normal acidity, *i. e.*, 46 per cent.; 30 per cent. a hyperacidity, and 23 per cent. a subacidity. Hyperacidity is proportionately more frequently observed in males and subacidity in females. In recent ulcers and especially those accompanied by recent hemorrhage, the acidity is very high, while in chronic forms the acidity is low.

7. The average duration of symptoms is twelve years.

8. The most prominent symptom of ulcer, pain, occurs in 94 per cent. of cases, and pain is most frequent in cases associated with a high acidity. Pain appears sometimes immediately after

the taking of food (gastric ulcer), and at times long after the taking of food (duodenal ulcer). In many instances there are one or more periods of intermission of pain as well as the other symptoms; these periods vary from one to many months.

9. An epigastric tender area is present in at least 90 per cent. of all cases, a dorsal tender area in 32 per cent.

10. Vomiting is a very prominent symptom occurring in 67 per cent. of cases.

11. Hematemesis is present in 22 per cent. of cases and melena in 51 per cent. Melena is more than twice as frequent as gastric hemorrhage. Occult blood is present in 81 per cent. of the cases.

12. Of the 1000 cases of ulcer, 52 per cent. are duodenal and 40 per cent. gastric; the largest proportion occurring in males (58 per cent.).

13. Of the duodenal ulcers, 48 per cent. present normal acidity, 35 per cent. hyperacidity, and 16 per cent. a subacidity; hyperacidity being more frequently observed in males and subacidity in females.

14. Pain is present in 96.5 per cent. of duodenal ulcers, and is most prominent in cases with hyperacidity.

15. Distinct periods of intermission from pain and other symptoms, varying from one to twelve months or more, are exceedingly common in this affection.

16. Epigastric tenderness is present in 89 per cent. of the duodenal cases; a tender area to the right or left of the median line in 7 per cent.

17. Vomiting occurs in 21 per cent. of duodenal cases, and is more frequent in those accompanied by high acidity.

18. Melena occurs in 54 per cent. of duodenal cases, and occult blood is found in the stools in 83 per cent.

19. Seventy-two per cent. of cases of peptic ulcers treated by the Leube treatment are cured, 66 per cent. by the Lenhartz, 47 per cent. by the ambulatory treatment administering nitrate of silver, 50 per cent. with subnitrate of bismuth, and 40 per cent. with olive oil. Of the cases treated by the Leube cure, 74 per cent. remained permanently well, while 77 per cent. of those treated by the Lenhartz cure, likewise remained permanently well.

20. Seventy-one per cent. of the cases operated on are cured, 91 per cent. remaining permanently well.

The diagnosis of ulcer is often most difficult. The diagnosis of typical cases is not difficult, but the atypical forms form a great proportion of cases, and great difficulty is often experienced in drawing conclusions concerning such cases. Some of the important symptoms, such as pain and epigastric tenderness as well as nausea, vomiting, hematemesis, and melena, may be absent, or may be so overshadowed by other symptoms as to become insignificant.

The diagnosis of ulcer should never be made without the detec-

tion of occult blood in the stools, and yet when we remember that occult blood may appear in many other conditions, and that even in ulcer it often disappears, especially when the ulcer is healing, the difficulties in diagnosis become even greater.

The diagnosis between duodenal and gastric ulcer is often very difficult and many clinicians consider it is impossible in many instances to differentiate between the two. It is generally admitted that pain appearing two hours or more after meals (hunger pain), is indicative of ulcer of the duodenum, while pain appearing early is gastric. Hemorrhage is mainly observed in the vomitus in gastric ulcer, and most frequently in the feces in duodenal ulcer, but is often observed in both in either condition, and is of but slight importance in distinguishing the two forms, unless blood is persistently observed in the feces without being present in the gastric secretion.

Peptic ulcers are frequently mistaken for gastric neuroses associated with hyperacidity, and it is of the greatest importance to distinguish between these conditions.

Gall-bladder disturbances are to be differentiated from duodenal ulcers, but the diagnosis between the two conditions is often very difficult and sometimes impossible.

There can be no question but that a large proportion of ulcer cases recover under medical treatment. According to our observations, 72 per cent. by the Leube cure, 66 per cent. by the Lenhartz cure; this is in comparison to 71 per cent. treated surgically. When an ulcer patient is treated medically, he should be thoroughly treated, and ambulatory treatment should never be instituted. As we have shown, the results of ambulatory treatment are exceedingly unsatisfactory, inasmuch as in but from 40 to 50 per cent. of cases so treated is a cure effected. I believe that many ulcer cases do not recover because the treatment is not sufficiently prolonged. A rest cure of but a few weeks is often insufficient. In severe cases the patient should be put to bed for six or eight or even more weeks. The answer to the question whether the Leube or the Lenhartz treatment should be undertaken, depends largely upon the patient and the severity of the symptoms. Quite satisfactory results are often obatined by the Leube cure, and at times on account of the persistent nausea, vomiting, and pain, one is forced to follow this form of treatment. It is best when possible, however, to institute the Lenhartz treatment, for a restriction to liquid food is often unnecessary and usually results in great weakness and exhaustion. The anemia too frequently found accompanying this condition is often very extreme and the small quantities of milk which are consumed cannot prevent the onset of rapid exhaustion and emaciation.

Surgical intervention should only be considered if medical treatment has been persisted in for a sufficiently long period of time,

and has not been found effectual; especially is it indicated in those cases accompanied by severe and persistent pain, vomiting, or hemorrhage, or in ulcers recurring, notwithstanding thorough medical cure. The operation is indicated too in all pyloric or duodenal ulcers accompanied by stenosis. In ulcers situated at other parts of the stomach operation gives but slight relief unless radical procedures (resection or excision) are undertaken. Operation should be promptly practised in all cases of perforation.

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## DIARRHEA OF GASTRIC ORIGIN: DIAGNOSIS AND TREATMENT.[1]

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In the study of gastro-intestinal disorders, chronic diarrhea is commonly classed among the conditions the cause of which may be obscure and the treatment, therefore, symptomatic and unsatisfactory. Diarrhea is a symptom and not a disease, and is to be regarded as the expression of a motor reaction of the intestines to irritants. The number and character of the irritant substances are many and varied—chemical, vegetable, and animal—while a purely functional diarrhea may occasionally ensue from an irritated nervous mechanism. Whatever the nature of the irritant in diarrhea, its action results in the production of a pathological acceleration of intestinal peristalsis. This increased peristalsis, in the majority of cases, is associated with some structural lesion in the walls of the intestine, but it may occur without such change. Furthermore, a diarrhea which owes its origin to the mere presence of irritants in the bowel contents may later be perpetuated by the development of definite anatomical changes in the intestinal mucosa. Such is probably the case in the form of diarrhea under discussion. It is the purpose of this article to direct attention to the clinical features of a not infrequent variety of diarrhea, the recognition of which should be simple in most cases, while the results of treatment are often brilliantly successful.

Diarrhea of gastric origin is dependent upon a condition of the stomach which may be either primary or in the nature of a reflex gastric disorder; most commonly a condition of anacidity, occasionally insufficiency of the pylorus, and rarely hyperchlorhydria. In the first two groups the food passes into the intestine insuffi-

[1] Read before the Johns Hopkins Medical Society, Baltimore, March 18, 1912.

ciently prepared by the usual gastric digestion and so acts directly as an irritant, or undergoes changes resulting in the production of irritant substances, while in cases of diarrhea associated with hyperacidity it is presumed that the entrance of the excessively acid secretion into the bowel is sufficient to set up increased peristalsis. The discussion in this article, however, is confined to the occurrence of diarrhea as a direct consequence of the failure of the stomach to produce its normal secretion of hydrochloric acid.

The term gastric anacidity is applied to those cases in which after an Ewald test breakfast there is no free hydrochloric acid and the total acidity does not exceed 20 "acidity per cent." It occurs in four groups of cases: (1) As a purely functional disturbance, either temporarily or over prolonged periods of time, with retained ferment secretions; (2) in achylia gastrica, a condition in which there is a permanent absence of all gastric secretions; (3) in pernicious anemia and certain metabolic disorders, as diabetes; and (4) in carcinoma of the stomach.

INCIDENCE. For purpose of analysis, I have made a statistical study of 500 patients in whom one or more gastric examinations were made. These cases are selected from my records of over 2000 private patients examined during the last four years in the course of general diagnosis work in internal medicine, not at all confined to diseases of the stomach. Gastric analyses were made only in cases presenting gastro-intestinal symptoms, or when such an examination seemed necessary to establish the diagnosis. For this reason the incidence of gastric anacidity to other lesions of the stomach cannot be exactly expressed. For example, cases of pernicious anemia that presented no difficulty in recognition were not necessarily submitted to gastric analysis, yet anacidity was undoubtedly present in every case. Of these 500 patients, 81, or 16.2 per cent., showed the condition of gastric anacidity. In a much larger series of 3147 patients, Kelling[2] reports 521 cases, or 16½ per cent. of anacidity. Of my 81 cases, 20 had cancer of the stomach, 22 were classified under the term neurosis, 5 were evident cases of chronic alcoholic gastritis, while the stomach findings in the remainder were associated with or regarded as reflex disturbances from the following conditions: Chronic appendicitis, 7 cases; cardiovascular disease and lesions of the female pelvic organs, each 4 cases; cholelithiasis, 3 cases; pernicious anemia, migraine, pellagra, pulmonary tuberculosis, and eyestrain, each 2 cases; and 1 case each of hysteria, peritoneal adhesions, benign tumor of stomach, myxedema, chronic influenza, and aural vertigo. One of the cases of chronic appendicitis was associated with definite hypothyroidism, and one of the pellagra cases was complicated with intestinal amebiasis. One patient, included above, had a

[2] Arch. f. Verdauungskrank., 1909, Band xv, Heft 5, p. 568.

ruptured ectopic pregnancy and pelvic hematocele, and this was accompanied by severe attacks of gastric tetany, with pronounced dilatation of the stomach, ending in recovery.

Diarrhea was a prominent symptom in 13 of these 81 cases, including the 2 pellagra patients. Excluding these 2 cases, and the patients with malignant disease of the stomach, there were in the remaining 59 cases of gastric anacidity 11 patients with diarrhea, or approximately 18½ per cent. These 11 cases form the basis of this article, and most of them occurred in the group of patients in whom no organic cause could be ascertained as being responsible for the anacidity. A brief synopsis of the histories of these cases follows:

REPORT OF CASES. CASE I.—*Clinical summary: Matutinal diarrhea for two months; marked loss of weight and strength; no abdominal symptoms; complicating peripheral (toxic) neuritis; gastroptosis; indicanuria; gastric anacidity on four examinations; prompt recovery from symptoms; gain of 46 pounds in two and one-half years, although condition of achylia persists.*

Mrs. B. (1030), aged fifty-four years. Date, September 20, 1908.

Complaint: Diarrhea and weakness.

Past history: General health good, 9-para. As a young woman was subject to attacks of "cholera morbus."

Present illness: Onset July 15, 1908, with loose bowels, and this condition has persisted ever since. Has lost 30 pounds; present weight 118. Has become distinctly weak, and fears she has either tuberculosis or malignant disease of the intestines. Has had no abdominal pain or cramps, but there has been a great deal of intestinal rumbling. The bowel movements occur for the most part in the early morning, generally number five or six, and then do not take place again until the following morning. The stools are always liquid, not particularly offensive, and have not contained any visible blood or mucus. Patient has had no fever, chills, or sweats. Appetite is poor, some nausea, no vomiting. No headaches. She is not a nervous woman. Several weeks ago she noticed that she was unable to flex the left foot when she put on her stocking, and now drags that foot slightly when walking. There is slight numbness below the left knee, but no pain in any of the extremities.

Examination: Complete physical examination of heart, lungs, deep reflexes, pupillary reactions, and glands is negative. Abdomen rather full and pendulous. The stomach on inflation is definitely enlarged and ptosed. No tenderness; no masses. Distinct weakness of anterior tibial group of muscles of left leg, with no sensory disturbances. Urine: The urine shows trace of albumin; indican much increased. Otherwise negative. Blood: Polymorphonuclear neutrophiles, 45 per cent.; small mononuclears, 46 per cent.; large mononuclears and transitionals, 8 per cent.; eosinophiles, 1 per

cent. No poikilocytosis; no nucleated red blood corpuscles; malarial parasites not present. Gastric analysis: Test breakfast removed in one hour; only a few cubic centimeters expressed. Free HCl, 0; lactic acid not present. Test breakfast repeated; removed in forty minutes; 85 c.c. obtained. Free HCl, 0; total acidity, 5; lactic acid not present.

December 17, 1908. Gastric analysis: Test breakfast, 20 c.c. removed in forty minutes. Free HCl not present.

January 8, 1909. Patient weighs 130½ pounds. For the last two months has had only one formed stool a day. Eats a general diet. No evidence of peripheral neuritis.

January 3, 1910. Patient weighs 153 pounds. Is perfectly well.

April 10, 1911. Patient weighs 164 pounds. Has never had any return of the diarrhea. Suffers more or less from vague pains about the larger joints. Urine continues to show great excess of indican.

December 30, 1911. Patient was requested to return for a gastric examination. This showed 60 c.c. expressed in forty-five minutes after an Ewald test breakfast. Clear, non-viscid fluid and coarsely divided bread particles; no visible blood or mucus. Free HCl, 0; total acidity, 6; lactic acid, 0; pepsin, 0; rennet ferment, 0. She says that she remains entirely free from any gastro-intestinal disturbances; bowels move once daily; stools almost always formed, and appear natural. Has had no nausea or flatulence. Has lost weight since last spring, and today weighs 152 pounds. Blood pressure, 182 mm. Hg.

Case II.—*Clinical summary: Periodical attacks of diarrhea for years; on two occasions blood and mucus in stools. Recently tendency to loose bowels without actual diarrhea; no history of constipation; chief complaint is of indigestion, with symptoms of gastric hyperacidity; gastric anacidity on four examinations; complete recovery.*

Mrs. W. (1212), aged thirty-eight years. Date, January 29, 1909.

Complaint: Stomach trouble.

Past history: Operation for pelvic abscess five years ago. Prior to that no serious indigestion except occasional "bilious spells."

Present illness: Beginning seven years ago, patient has had irregular attacks of diarrhea, one of which lasted four months. On two occasions there was blood and mucus in the stools. For the last four months the bowels have had a tendency to be loose, without actual diarrhea. No history of constipation. Patient is subject to indigestion, characterized by pain occurring twenty minutes to half an hour after meals; it becomes worse during the next half hour, then gradually disappears. This pain is a sharp aching and burning, and is always intensified if patient eats acid fruits. Occasional nausea, no vomiting. No relief of pain by eating. Frequent abdominal distention and diffuse soreness.

Patient says that her symptoms are always worse when she is worried or nervous, while at other times she suffers very little from her stomach.

Examination: Heart, lungs, abdomen, superficial glands, and deep reflexes negative. Blood pressure, 110 mm. Urine, negative. Blood: Polymorphonuclear neutrophiles, 75 per cent.; small mononuclears, 19 per cent.; large mononuclears and transitionals, 5 per cent.; eosinophiles, 1 per cent. Moderate anisocytosis; no nucleated red blood corpuscles; malarial parasites not present. Gastric analysis: Test breakfast removed in fifty minutes; 80 c.c. expressed. Free HCl, 0; total acidity, 4; lactic acid not present.

February 13. Gastric analysis: Test breakfast removed in forty-five minutes; 20 c.c. obtained. Free HCl not present.

March 10. Gastric analysis: Test breakfast removed in forty-five minutes; amount, 60 c.c. Free HCl, 0; lactic acid not present.

April 21. Gastric analysis (specimen sent by mail): Test breakfast, 5 c.c. submitted. Free HCl not present.

Patient remained under treatment for six weeks, then left for her home in West Virginia. It is interesting to note that the pain in the epigastrium entirely ceased while patient was taking 3 drams of dilute HCl daily. A letter received on May 24, 1909, says that she feels perfectly well, and that her weight has increased from 138 to 157 pounds. In July, 1910, patient called while in the city and said that she remained in the best of health. No further gastro-intestinal symptoms. A letter received from her on January 2, 1912, states that she continues to be entirely well.

CASE III.—*Clinical summary: Alternating diarrhea and constipation for three years, following severe attack of grip; bowels generally loose; matutinal diarrhea; no abdominal symptoms except flatulence; extreme weakness; stomach not enlarged or displaced; gastric anacidity; trichomonads in stools; good recovery.*

Mrs. T. (1335), aged sixty-three years. Date, April 26, 1909.

Complaint: Intestinal indigestion.

History: Patient says that she has never been very robust. Three years ago had four severe attacks of grip, and was ill the whole winter. Dates the onset of her bowel trouble to this illness. At times the bowels are constipated, but, as a general rule, are very loose. Frequently has eight or nine stools a day, which consist of nothing but water. Stools occur chiefly in the early morning. Has a good deal of gas in the bowels, but has suffered no abdominal pain. Has not lost weight, but has become extremely weak; can hardly walk. The diarrhea is always worse in the summer. Has had short periods of constipation, and on one occasion a fecal impaction, attributed to astringent medicine.

Examination: Poorly nourished woman. Skin dry. Complexion sallow, not cachectic. Blood pressure, 152 mm. Heart, lungs, deep reflexes, glandular system, pupillary reactions and rectum

negative. Blood: Polymorphonuclear neutrophiles, 51 per cent.; small mononuclears, 32 per cent.; large mononuclears and transitionals, 13 per cent.; eosinophiles, 4 per cent. Negative for malaria. Stool: Liquid; brownish green; moderate excess of mucus; no visible blood; many active trichomonads; no amebæ or other parasites. Gastric analysis: Test breakfast, 12 c.c.; expressed in one hour. Free HCl, 0; total acidity, 3; lactic acid not present.

Patient was treated in the hospital sixteen days and the bowels became constipated as soon as HCl was administered. She was seen at her home in a distant city about the last of December, 1909, and was last seen in April, 1911. Says that she remains perfectly well, eats heartily of general diet, and has had no return of the diarrhea.

CASE IV.—*Clinical summary: Patient says that her bowels are always "weak" and that she has "dysentery" every summer; much mucus in the stools, at times some blood; chief symptoms due to marked visceroptosis; gastric anacidity; improved under treatment.*

Mrs. C. (1450), aged thirty-nine years. Date, August 1, 1909.

Complaint: Pain in back, right side, and lower abdomen.

History: Patient says that her digestion is "quite good considering all she has the matter with her." Appetite good. Occasional attacks of "biliousness," associated with sick stomach and vomiting, but these only occur in the summer. Has had no sour stomach, no belching, but has a good deal of gas in her abdomen with rumbling. Suffers with "dysentery" every summer, but is not laid up with it. At these times has blood and mucus in the stools. Her principal complaint is of severe backache, pain in both flanks, and in the lower abdomen; feels as if everything would drop out of her when she stands. No history of cramp colic.

Examination: Heart, lungs, glandular system, and deep reflexes negative. Abdomen shows thin walls and visible peristalsis. The stomach on inflation much enlarged and displaced. The whole right kidney is easily felt. Slight diffuse abdominal tenderness, but no masses. Skiagraph after administration of bismuth shows that the pylorus lies just to the right of the navel; lesser curvature passes below the navel and upward on the left side parallel to the spine; the greater curvature reaches almost to the symphysis pubis. Gastric analysis: Test breakfast removed in one hour; 9 c.c. obtained. Free HCl, 0; total acidity, 6; lactic acid not present.

Patient was treated in the Johnston-Willis Hospital for six weeks. Distinctly improved. Adhesive straps applied to the abdomen which afforded much relief.

December 23, 1909. Patient has gained 20½ pounds; continues to wear adhesive straps to the abdomen; much improved in strength, with relief of abdominal symptoms.

CASE V.—*Clinical summary: Patient awakened early every morning by intestinal discomfort and rumbling, followed by loose stools; onset attributed to attack of grip two years ago. Appendectomy without relief of symptoms; no pronounced diarrhea, but stools never formed; gastric anacidity on five examinations; gradual recovery from symptoms, although the achylia persists.*

Mr. R. (1646), aged thirty-eight years. Date, January 14, 1910.

Complaint: Discomfort in abdomen.

History: Patient had grip early in 1908, and his health has not been good since that time. Began to suffer with the bowel trouble of which he now complains. In October, 1908, the appendix was removed without amelioration of any of his symptoms. He had had one sharp attack of acute appendicitis three and one-half years before his operation. Patient complains chiefly of bad nights. Usually goes to sleep promptly, but is always awakened about 5 or 6 o'clock with a grumbling and uncomfortable feeling in the abdomen, especially over the bladder, which is always relieved by defecation. Complains very much of gurgling in the abdomen, and has a general peristaltic unrest. Has one or two stools before breakfast and one shortly after this meal. Stools are rarely formed, otherwise appear natural. Has passed no blood or mucus and has had no tenesmus. On rare occasions has short periods of constipation. Appetite quite good. No gastric symptoms. Complains of chronic fatigue and a variety of nervous symptoms. Average weight prior to appendectomy was 135 pounds; today he weighs 152 pounds.

Examination: Complete physical examination negative. Blood pressure, 146 mm. Stomach not displaced or enlarged. Urine negative. Gastric analysis: Test breakfast removed in forty-five minutes; 30 c.c. obtained. Free HCl, 0; total acidity, 3; lactic acid not present. Stool: Negative except for moderate number of fatty acid crystals. Blood: Polymorphonuclear neutrophiles, 59 per cent.; small mononuclears, 31 per cent; large mononuclears and transitionals, 9 per cent.; eosinophiles, 1 per cent. Negative for malaria.

April 7, 1910. Gastric analysis: Test breakfast removed in fifty minutes; 70 c.c. expressed. Free HCl, 0; lactic acid, not present.

June 1, 1910. Patient is definitely better but still has occasional attack of loose bowels in the early morning. Is discouraged about his condition.

Patient was sent to the Johns Hopkins Hospital, Baltimore, in July, 1910, and a letter from Dr. T. R. Boggs states that his findings correspond to those already mentioned and that the patient shows an absence of free HCl and very low total acid. It was noted that patient's tolerance for fat was somewhat low, although he took a free diet without fat loss.

March 10, 1911. Complete physical examination negative as before; weight, 134 pounds. Blood pressure, 155 mm. Urine, negative except for great increase of indican. Gastric analysis: Test breakfast removed in forty-five minutes; 140 c.c. expressed. Free HCl, 0; total acidity, 5; lactic acid not present. Patient is blue and depressed, but continues at his business. Bowels move once or twice early in the morning; stools generally formed. Continues to complain of gas and rumbling in the lower abdomen, which awakens him every morning at 3 or 4 o'clock.

December 18, 1911. At my request patient returned today for a stomach examination. He says that he is practically well, and has stopped worrying about himself now that he has learned to realize that his illness will not terminate fatally. Looks well; weighs 147 pounds. Has been taking 30 drops of the tincture of nux vomica before meals for two years, and HCl after meals for the same length of time. For the last eight months has substituted tablets of acidol with pepsin for the official HCl. Has absolutely no gastric symptoms. Bowels generally move once a day, and the stools are formed and appear natural. Occasionally has some aching "in the bowels" when he awakens in the morning, and at these times has some pain in the bladder. Has very little flatulence. Says that meat does not agree with him, but with the exception of this he eats a general diet and drinks buttermilk regularly. Blood pressure, 142 mm. Hg.

Gastric analysis: Test breakfast removed in forty-five minutes; 100 c.c. expressed. Free HCl, 0; total acidity, 2; lactic acid, 0; peptone, 0; pepsin, 0; rennet ferment, 0; erythrodextrin, 0.

CASE VI.—*Clinical summary: Persistent matutinal diarrhea for three years; gastric anacidity on three examinations; diarrhea ceased after administration of HCl with resulting constipation; trichomonads in feces; visceroptosis; arterial hypertension; continued nervous depression.*

Mrs. H. (1932), aged fifty-five years. Date, June 27, 1910.

Complaint: Diarrhea, weakness, and nervousness.

History: Patient has always been nervous. Suffered from a severe attack of nervous prostration twelve years ago. For the last three years has had a chronic diarrhea, characterized by four or five watery stools early each morning, with no actions during the rest of the day. Complains of frequent headaches, nervousness, and weakness. Appetite poor. Has lost considerable weight.

Examination: Enlarged heart, associated with mitral regurgitation. Blood pressure, 165 mm. Right kidney extremely movable. Area of gastric tympany increased and displaced downward; the greater curvature reaches 2½ inches below the umbilicus. Physical examination otherwise negative. Urine, negative. Indican not increased. Blood: Leukocytes, 5500. Negative for malaria. Differential count: Polymorphonuclear neutrophiles, 64 per cent.;

small mononuclears, 16 per cent.; large mononuclears and transitionals, 11 per cent.; eosinophiles, 9 per cent. Stool shows undigested milk curds; small bits of mucus; no visible blood; many trichomonads present; no other parasites. Gastric analysis: Test breakfast removed in forty-five minutes; 30 c.c. obtained. Free HCl, 0; total acidity, 5; lactic acid present.

July 23. Gastric analysis: Test breakfast removed in fifty minutes; 5 c.c. expressed. Free HCl, 0; lactic acid not present. Patient's diarrhea, which had previously been but poorly controlled with bismuth, stopped immediately on the administration of HCl. Patient spent several months at Clifton Springs Sanitarium during the summer of 1910. Shortly after this she had several attacks, apparently crises of arterial hypertension, the blood pressure rising to 200 mm.

May, 1911. Patient remains obstinately constipated, continues in a depressed nervous condition. Blood pressure varies from 160 to 170. No gastric symptoms except flatulence.

CASE VII.—*Clinical summary: Periodical loose bowels for two years; diarrhea for one month; pronounced secondary anemia; mitral regurgitation; weakness; no loss of weight; no gastric disturbances; abdomen negative; gastric anacidity; diarrhea ceased promptly under treatment.*

Mrs. D. (2014), aged forty years. Date, October 18, 1910.

Complaint: Weakness and diarrhea.

History: Shortness of breath on exertion for fifteen years, quite pronounced recently. Moderate edema of ankles for four years. Appetite good. No gastric symptoms. For the last two years, short periods of diarrhea. No history of constipation. Onset of bowel trouble followed directly upon an attack of "typho-malarial fever." One month ago bowels became loose and have continued so ever since. Stools vary in appearance, usually watery; six to eight a day. Most of the bowel movements occur in the early morning, but also move in the afternoon. Patient has had some tenesmus, but has observed no blood or mucus in the stools.

Examination: Mucous membranes pale. Complexion, sallow; slight cyanosis. Marked pyorrhea. Blood pressure, 152 mm. Heart moderately enlarged. Mitral regurgitation. Lungs, negative. Spleen, palpable. Blood: Red blood corpuscles, 2,992,000; leukocytes, 6200; hemoglobin, 41 per cent. Differential count: Polymorphonuclear neutrophiles, 70 per cent.; small mononuclears, 14 per cent.; large mononuclears and transitionals, 13 per cent.; eosinophiles, 1 per cent.; mast cells, 2 per cent. Considerable anisocytosis; no poikilocytosis; no basophilic degeneration; no nucleated red blood corpuscles; malarial parasites not present. Urine, negative. Indican not increased. Stools were negative on two examinations. Gastric analysis: Test breakfast removed in

fifty minutes; 60 c.c. expressed. Free HCl, 0; total acidity, 3; lactic acid not present.

January 3, 1912. Patient was asked to return for observation but declined to have another gastric examination. She followed the treatment as outlined for about two months and the diarrhea ceased promptly and has not recurred. She says she is in much better health, but is still very anemic. Has no indigestion of any kind. Has gained 12 pounds in weight. Chief symptoms now referable to her anemia and heart lesion, but has had no further edema of the extremities. Blood: Red blood corpuscles, 3,568,000, leukocytes, 8600, hemoglobin, 43 per cent.. Differential count: Polymorphonuclear neutrophiles, 62 per cent.; small mononuclears, 25 per cent.; large mononuclears and transitionals, 11 per cent.; eosinophiles, 2 per cent. Red blood corpuscles show considerable variation in size and the majority of the cells are pale. No poikilocytosis, no basophilic degeneration, no nucleated red blood corpuscles. Malarial parasites not present.

CASE VIII.—*Clinical summary: Prolonged periods of matutinal diarrhea for four and one-half years; several times cured by administration of HCl; recurrences following acute illnesses; gastric anacidity on three examinations; at times mucus in stools associated with abdominal cramps; prompt recovery on treatment.*

Miss P. (2044), aged thirty years. Date, November 9, 1910. Complaint: Diarrhea.

Onset of present illness April, 1906, prior to which time she had been perfectly well. Contracted a severe case of measles complicated by bronchitis. Bowels became loose at that time. Patient consulted me in the fall of 1907 and two stomach examinations showed a condition of gastric anacidity which was thought to be responsible for her intestinal disturbance. Patient took HCl for three months and remained perfectly well for a year. Says that she was strong and fat. Then contracted bronchitis, followed by a return of the diarrhea. This has continued ever since at irregular intervals. Last fall patient was perfectly well for several months. Diarrhea began again in January of this year and lasted until March, returned in June. Patient has frequently been confined to her bed with it. The diarrhea always occurs early in the morning and forenoon; practically never has any bowel action after mid-day. Has had as many as fifteen stools a day, which were watery and yellow in color. She is always able to recognize any vegetable she may have eaten. At times has had considerable mucus in the stools and on these occasions suffers with griping pains which cease when the bowels move. No gastric disturbance except occasional nausea.

Examination: Complete physical examination negative. Patient is a well-developed woman. Stomach on inflation slightly enlarged but not ptosed. Blood: Polymorphonuclear neutrophiles,

54 per cent.; small mononuclears, 25 per cent.; large mononuclears and transitionals, 21 per cent. Negative for malaria. Urine, negative except for marked increase of indican. Gastric analysis: Test breakfast removed in forty-five minutes; 30 c.c. expressed. Free HCl, 0; total acidity, 9; lactic acid present. Stool shows numerous small flakes of mucus, but is negative for ova and parasites.

March 7, 1911. Patient called today while in the city to say that she remains perfectly well. Continued treatment until three weeks ago. Has gained 15 pounds in weight. Bowels are regular and she has one formed stool each morning.

CASE IX.—*Clinical summary: Moderate diarrhea for six months; preceding history of constipation; onset with fever; no abdominal pain or gastric symptoms; moderate anemia; weakness and loss of weight; gastric anacidity on two examinations; arteriosclerosis; pronounced improvement on treatment.*

Mr. P. (2101), aged sixty-one years. Date, December 16, 1910.

Complaint: Weakness and loose bowels.

History: No history of indigestion until six months ago. Last June had slight fever and began to suffer with loose bowels. Diarrhea continued until the middle of October, averaging two or three stools a day. Began to lose weight. Had no special indigestion. Then caught cold; became depressed; had some fever. Blood was examined, and was told he had malaria; took quinine. Has had no fever in the last three weeks. Says that his digestion and appetite are good, but he is afraid to eat because his bowels are loose.

Examination: Complete physical examination negative except that his blood pressure is 156 mm. with accentuation of the second aortic heart sound. Stomach slightly enlarged. Urine: Specific gravity, 1.014; albumin, distinct trace; indican, slightly increased; occasional hyaline and finely granular cast, otherwise negative. Blood: Hemoglobin, 76 per cent. Differential count: Polymorphonuclear neutrophiles, 72 per cent.; small mononuclears, 24 per cent.; large mononuclears and transitionals, 4 per cent.; eosinophiles, 0 per cent. Negative for malaria. Stool, negative for ova and parasites. Gastric analysis: Test breakfast removed in fifty minutes; 10 c.c. expressed. Free HCl not present.

April 21, 1911. Patient reports that his general condition is greatly improved. Has gained 11½ pounds in weight. Bowels move twice a day. Occasionally the actions are loose but whenever they are so he takes full doses of HCl and immediately they become formed again. Says he has no indigestion. His spirits are much better. Is greatly encouraged about himself. Blood pressure, 145 mm. Blood: Hemoglobin, 82 per cent. Differential count: Polymorphonuclear neutrophiles, 72 per cent.; small mononuclears, 22 per cent.; large mononuclears and transitionals, 6 per

cent.; eosinophiles, 0 per cent. Negative for malaria. Urine: Specific gravity, 1.022; albumin, faint trace; indican greatly increased; occasional hyaline cast. Gastric analysis: Test breakfast removed in forty minutes; 50 c.c. expressed. Free HCl, 0; total acidity, 18; lactic acid not present.

CASE X.—*Clinical summary: Patient awakened early in mornings with pain in her back and abdomen; matutinal diarrhea for several months, associated with flatulence; no gastric symptoms; gastric anacidity; complete recovery.*

Mrs. N. (2526), aged thirty-five years. Date, August 1, 1911.

Complaint: Pain in the back and abdomen.

History: No acute infections or serious illness until four and one-half years ago, when she had a severe attack of "erythema nodosum" when three months pregnant, which confined her to bed for seven weeks. Nine days after labor she had two chills and high fever, which persisted for two weeks. For five months after the birth of this child she suffered with symptoms similar to those of the present illness, but otherwise has been well, and bowels have always been regular. Onset of present illness was in March, 1911, after patient had been through a severe nervous strain nursing her sick mother. Began to suffer with a dead, aching pain in the small of the back radiating forward into the abdomen; never acute; not very noticeable during the day, and she rarely goes to bed with it. The pain generally awakens her about 4 or 5 o'clock in the morning. For the last few months her bowels have been loose, the first stool occurring about 5 A.M., and the bowels move again three or four times during the morning. The stools are large and watery, not offensive, and have contained no blood or mucus. Associated with this there has been a great deal of gas and rumbling in the abdomen which makes her nervous. On two or three occasions recently has been slightly nauseated; no other gastric symptoms. Appetite good, but patient has been dieting and her weight has diminished from 160 to 145.

Examination: Complete physical examination negative. Patient is a well-nourished and healthy looking woman. Blood pressure, 108 mm. No visceroptosis. Slight tenderness on deep pressure over the sigmoid and the head of the cecum. Blood: Polymorphonuclear neutrophiles, 56 per cent.; small mononuclears, 31 per cent.; large mononuclears and transitionals, 11 per cent.; eosinophiles, 2 per cent. Negative for malaria. Urine, negative; indican not increased. Gastric analysis: Stomach found empty forty-five minutes after test breakfast. Test breakfast repeated; removed in thirty minutes; 40 c.c. expressed. Free HCl, 0; total acidity, 3; lactic acid present.

December 30, 1911. Patient reports from her home in North Carolina that she is perfectly well and fears she is getting too stout.

CASE XI.—*Clinical summary: Slight digestive disturbance for some years associated with constipation until three years ago; at that time had severe attack of biliary colic, with a second similar attack last summer; for the last three years persistent loose bowels in the early mornings; considerable flatulence; gastric anacidity on three examinations; operation showed chronic cholecystitis with one large gallstone and chronic appendicitis; recovery.*

Mrs. F. (2660), aged forty-four years. Date, Novermber 6, 1911.

Complaint: Abdominal pain and indigestion.

History: At the time of the patient's marriage, eighteen years ago, she was thin and run down and had considerable indigestion for two years. Does not recall her symptoms, but had no abdominal pain, except one acute attack seventeen years ago, diagnosticated as appendicitis. No history of typhoid or other acute infections. Has complained of slight "indigestion" for years. Appetite good and regular; no nausea or vomiting, but has had considerable gas, which has caused bloating and pain. No pyrosis; no sour stomach or regurgitation of food. Bowels always constipated until the present illness. Onset of present illness three years ago, with severe attack of biliary colic. Her husband, a physician, says that ever since then she has had threatened attacks. A second severe attack occurred last summer. For the last three weeks the patient has suffered with a heavy aching in the epigastrium, coming two or three hours after eating. This has been relieved by induced vomiting, and the food has returned entirely undigested. For the last three years the bowels have been persistently loose, and at times watery, attributed in part to "cholelith pills," but also occurring independently of any cathartic medicine. Has averaged three or four stools a day; bowel movements almost invariably confined to early morning hours. Stools rather pale at present time; have contained no blood or mucus. No loss of weight. Two recent gastric analyses made by her husband have showed an anacidity without evidence of stasis.

Examination: Well-nourished woman; moderately anemic; no jaundice. Heart, lungs, pupillary reactions, deep reflexes, and glandular system normal. Blood pressure, 114 mm. Abdomen shows thick panniculus; stomach on inflation slightly enlarged but not ptosed. Decided tenderness on deep pressure overhead of cecum. Slight tenderness beneath the right costal border, but no gall-bladder block elicited. Urine: Distinct trace of albumin and great excess of indican; otherwise negative. Blood: Hemoglobin, 78 per cent. Differential count: Polymorphonuclear neutrophiles, 60 per cent.; small mononuclears, 34 per cent.; large mononuclears and transitionals, 4 per cent.; eosinophiles, 2 per cent. Negative for malaria. Gastric analysis: Test breakfast removed in forty-five minutes; 100 c.c. expressed. Free HCl, 0; total acidity, 2; lactic acid present.

November 25, 1911. The diagnosis of chronic cholecystitis with probable chronic appendicitis having been made, patient was operated upon today at the Johnston-Willis Sanatorium. The appendix was thickened; had a club-shaped extremity, and was removed. The gall-bladder was greatly thickened and contracted with many adhesions about it. Contained about one ounce of pus, and one large solitary calculus was withdrawn from the cystic duct.

December 17, 1911. Patient was discharged well. Diarrhea began about a week after operation, but was controlled at once by administration of HCl.

The following case is reported because of its special interest, but is not included in the statistics for the reason that a gastric analysis was not obtained:

CASE XII.—*Clinical summary: Matutinal diarrhea of seven years' duration; onset following grip; trichomonads in stools but repeated examinations negative for other parasites; appendicostomy four years ago without relief; prolonged treatment with various intestinal antiseptics and restricted diet; gastric analysis not obtained; prompt recovery on administration of HCl.*

Mrs. K. (2179), aged fifty years. Date, January 19, 1911.

Complaint: Chronic diarrhea.

History: Seven years ago patient visited New Orleans. Shortly after this had an attack of grip, following which the bowels became loose and the diarrhea has continued ever since. She feared that she had contracted amebic dysentery in the South. Four years ago appendicostomy was done, although no amebæ had been demonstrated in the stools. Trichomonads were present on several examinations. Bowels irrigated through the appendix, with various solutions, without improving the intestinal condition, and after some months the wound was allowed to close. At present, the patient is on a limited diet. Says that she suffers from distressing intestinal peristalsis for an hour before rising in the morning. Generally has one stool before breakfast, and then has two or three stools after breakfast, generally goes to stool directly after lunch. The bowel movements are usually brown in color, loose or watery. Has passed considerable mucus at times. Patient suffers from soreness and a dragging in the bowels. No gastric symptoms.

Examination: Complete physical examination negative. Blood pressure, 154 mm. Spleen, palpable. Blood: Hemoglobin, 88 per cent. Differential count: Polymorphonuclear neutrophiles, 64 per cent.; small mononuclears, 28 per cent.; large mononuclears and transitionals, 5 per cent.; eosinophiles, 2 per cent.; mast cells, 1 per cent. Negative for malaria. Urine: Specific gravity, 1.018; albumin, distinct trace; indican, much increased; occasional hyaline cast. Stools show considerable number of trichomonads,

but no other parasites. Gastric analysis was attempted and the stomach found empty when the tube was passed. Patient refused to take a second test breakfast.

Treatment was outlined on the supposition that the diarrhea was secondary to a gastric anacidity. In May, 1911, patient reported that she took HCl regularly for three weeks and at irregular intervals since. The diarrhea has entirely ceased. Has had no further intestinal disturbance to the present time.[3]

SYMPTOMATOLOGY. The gastro-intestinal symptoms associated with the condition of gastric anacidity vary considerably in different individuals. While most of these patients suffer with symptoms referable to the stomach, yet in a certain proportion the complaint is entirely confined to the state of the bowels, and in a still smaller number of patients gastric anacidity exists with absolutely no symptoms on the part of the gastro-intestinal tract. In this series of 81 cases of gastric anacidity there were several instances of very minor digestive disturbances. In 3 patients, however, there was no history whatever of symptoms referable either to the stomach or the bowels. One of these patients was a gentleman of splendid physique, aged forty-one years, whose only complaint was susceptibility to head colds; another patient was a young society matron who became run down after a season of gayety and feared she had contracted tuberculosis; and the third case was a business man, aged forty-four years, a hard worker, never taking vacations, who complained of being always tired and irritable.

In several studies on achylia gastrica by various authors, cases have been reported in which a complete lack of gastric secretion has persisted for many years without apparent detriment to the general health. Such patients may present no subjective symptoms whatever, can take any form of food without discomfort, and the small intestine assumes vicariously the function of the stomach. Friedenwald[4] mentions a case in which gastric anacidity had persisted for twelve years, with gain in weight, and with but few attacks of intestinal disturbance. He also quotes Ewald's case, in which there was absence of gastric secretion for two and one-half years, during which time the patient gained 42 pounds in weight. Case I in my series—a patient with achylia gastrica—increased 46 pounds in weight in two and one-half years. Einhorn[5] reports a similar case that was under observation for four years. Thus it is evident, as Einhorn has indicated, that patients with gastric anacidity may be divided into three groups,

[3] This patient was seen in June, 1912. She said that a gastric analysis made at the Johns Hopkins Hospital January, 1912, showed no free hydrochloric acid and an absence of pepsin and rennet ferment. Her diarrhea remains entirely controlled by the continuous use of small doses (10 drops) of dilute hydrochloric acid after meals, but recurs as soon as the acid is discontinued.

[4] Osler's Modern Medicine, v, 157, Lea & Febiger, 1908.

[5] Diseases of the Stomach, 1906, fourth edition, p. 375.

according to (1) absence of gastro-intestinal symptoms; (2) symptoms mainly gastric, and (3) symptoms chiefly intestinal.

In a series of 112 cases of anacidity studied by Friedenwald[6] there were 8 patients presenting no gastro-intestinal symptoms; 69 patients complaining of a greater or lesser variety of gastric symptoms; and 35 patients having apparently no gastric symptoms but presenting marked intestinal disturbances. Just what factor comes into play to bring on the diarrhea is not always evident, but it is of interest to note that in 6 of my cases the patients dated the onset of the diarrhea to some acute illness (Cases III, V, VII, VIII, IX, and XII).

Clinical Features. The clinical features of diarrhea secondary to gastric anacidity are clear cut and definite in the majority of instances, so that not infrequently the diagnosis can be suspected before the stomach analysis is made. The leading symptoms may be enumerated as follows:

1. Diarrhea: The most striking feature of the diarrhea is its occurrence early in the morning and during the forenoon. As a rule it may be said that patients with this condition are unlikely to have any bowel movements in the afternoon or at night. This matutinal diarrhea often awakens the individual from sleep at 5 or 6 o'clock in the morning, a second call to stool generally occurs before breakfast, and one to three bowel movements take place between breakfast and the mid-day meal. In other patients the diarrhea is more profuse, with very frequent stools. Even so, the trouble is generally through for the day by the time luncheon is reached, as in Case VIII, with as many as fifteen stools a day. In some cases the diarrhea may alternate with constipation, but often the constipation may be attributed to full doses of astringent drugs, with which these patients are so often treated.

2. Character of the stools: The bowel movements are liquid and inoffensive, as a rule, and show the presence of macroscopic particles of undigested food, especially fruit and vegetables. In other cases the stools are soft and yellow, and show an excess of fatty acid crystals. Mucus and blood are not usually seen, but may occur during exacerbations of the symptoms. The presence of trichomonads was noted in 3 of my cases (III, VI, and XII).

3. Flatulence and peristaltic unrest is the rule, especially in the early morning hours. With this there may be griping pains throughout the abdomen, although most patients are free from actual abdominal pain. Irritability of the bladder, relieved after defecation, is not uncommon. This was so pronounced in Case V that the patient kept insisting that his kidneys must be diseased.

4. Gastric symptoms are often lacking or are overshadowed by the condition of the bowels. The entire absence of any com-

[6] Loc. cit.

plaint referred to the stomach is rather striking in this group of cases. The appetite is generally unimpaired, although the patient may be afraid to eat. Occasionally there is slight nausea, and, curiously enough, as in Case II, the patient may recite the symptoms of hyperchlorhydria.

5. Loss of weight and strength may develop quickly after the intestinal disturbance sets in. In other cases, with distinct weakness and prostration, there may be no diminution of the body weight. Early in the disease, and in the absence of complications, the patient does not look ill. Other individuals may show a marked secondary anemia, as in Case VII, but quite distinguishable from the blood picture of pernicious anemia.

6. Indicanuria is pronounced in most cases. Muscular pains and slight recurring arthritis are not uncommon, or there may be a definite neuritis, as in Case I. In the treatment of such cases the administration of hydrochloric acid has as specific an action as the salicylates in acute rheumatic fever.

7. Appearance of the test breakfast: In these cases of gastric anacidity the ingested food makes a relatively short stay in the stomach. This organ empties itself so quickly that often no remains of the Ewald test breakfast can be obtained after the lapse of one hour. This is easily accounted for by the absence of the normal "acid control" reflexly exerted over the pylorus by the first portion of the duodenum.[7] It is advisable to pass the stomach tube in forty or forty-five minutes after the breakfast has been taken. The material obtained shows a characteristic gross appearance. The bread particles are coarsely divided and show no evidence of having been acted upon by any digestive agent, and the fluid portion is clear, thin, and colorless, without visible blood or mucus. The usual tests for the presence of free HCl are negative, and the total acidity is usually below 10 "acidity per cent." Lactic acid, while generally absent, may be present in a distinct amount even in cases showing no evidence of stasis (Cases VI, VIII, X, and XI).

Prognosis. The prognosis of diarrhea secondary to gastric anacidity depends very largely upon the condition of the bowel wall, and this in turn rests upon the duration and intensity of the accompanying bacterial infection. The regular and normal secretion of hydrochloric acid by the healthy stomach is classed by Herter[8] as one of the defensive actions of the body against bacterial invasion. When the hydrochloric acid secretion is deficient, not only does the ingested food pass into the intestines in coarse "undigested" particles, but it carries with it a host of accidental, saprophytic forms of bacterial life, which immediately come into contact with the "obligate" and well-adapted parasitic

[7] W. B. Cannon, The Mechanical Factors of Digestion, Chapter IX, The Acid Control of the Pylorus, New York, 1911.

[8] The Common Bacterial Infections of the Digestive Tract, 1907.

forms of the intestinal tract. Hence, regarded in a certain light, hydrochloric acid is our best intestinal antiseptic. In his work on the infections of the digestive tract, Dr. Herter has shown that the absence of free hydrochloric acid is a feature of nearly all cases of pronounced saccharo-butyric putrefaction. He also believes that in all such cases the mucous membranes of the digestive tract are almost constantly in a state of excessive irritation, so that stimuli which in normal people would meet with little response give rise to excessive peristalsis and diarrhea. Thus, very clearly, a vicious circle is established.

W. Soltau Fenwick refers to the vicarious action of the intestines in the light of a compensatory adjustment, which is effective over a greater or lesser length of time and then is followed by a characteristic train of symptoms when this process of compensation begins to show signs of failing. The course of events is well expressed in his own words:[9] "In cases of diminished gastric acidity, peptic digestion is seriously interfered with, but a much larger proportion of starch is converted into sugar, and the work of the intestine in this respect is lessened. Although this condition is attended by a corresponding diminution in the amount of bile and pancreatic juice, compensation remains complete, owing to the fact that less alkali is required for neutralization and consequently a greater proportion remains available for the digestion of proteids and fats. The intestinal secretions also vary both in quantity and quality, with the composition of each meal; an excess of starch or proteids being productive of increased amylolytic or tryptic activity, while a diet composed largely of fat chiefly stimulates the secretion of bile and steapsin. These automatic adjustments may continue to work with perfect precision for a considerable time, but sooner or later the functions of the small intestine and other digestive glands become exhausted, and the processes of compensation begin to exhibit signs of failure. Under these circumstances fat is usually the first constituent of the food to suffer, and its diminished absorption is evidenced by an increased evacuation of neutral fats and combined fatty acids. Subsequently the proteids undergo excessive putrefaction and finally, the carbohydrates are decomposed by bacterial action and the production of sugar is arrested. This failure of compensation naturally occurs at an earlier date when the gastric disorder arises from organic disease. Thus, when subacidity ensues from chronic gastritis the intestine becomes hampered not only by the products of abnormal fermentation, but also by the presence of bacteria, and consequently intestinal inflammation, accompanied, perhaps by an infection of the biliary or pancreatic ducts, almost invariably develops and seriously interferes with the functions of digestion.

[9] W. S. Fenwick, Dyspepsia; Its Varieties and Treatment, 1910, p. 415.

In like manner, a continuous and excessive hyperacidity of the gastric juice tends to exhaust the activity of the pancreas and to excite a form of chronic intestinal inflammation which eventually arrests the solution and absorption of food."

TREATMENT. The essential point in the treatment of patients with the condition of gastric anacidity is the administration of large amounts of hydrochloric acid. The usual dose of 10 or 15 drops of the official dilute hydrochloric acid is inefficient. In these cases hydrochloric acid is not to be regarded as a drug. Its administration is for the sole purpose of supplying artificially a substance which the normal stomach secretes regularly and in good quantity. Not only is this acid indispensable for the activation of pepsinogen into pepsin, but on reaching the duodenum it serves as a hormone, or chemical messenger, to initiate the flow of pancreatic secretions.[10] Furthermore, hydrochloric acid may be regarded in a certain sense, as the most effective intestinal antiseptic, as I have already indicated. The only obstacle presented in the use of this acid is the difficulty of giving it to our patients in sufficient amounts. The mucous membranes of the throat will tolerate only weak solutions, hence the necessity of much fluid as a diluent. It is my custom, however, to prescribe 30 drops of the official dilute hydrochloric acid in a full glass of water one-half hour after meals, to be repeated again in one-half hour, or a total or 180 drops per day. On occasions, during the last year, I have substituted for the mineral acid, tablets of acidol. This is an ingenious synthetic product, hydrochloride of betain, a substance derived from molasses in the manufacture of beet sugar. When dissolved in water, or in the stomach, acidol gradually liberates hydrochloric acid. The only objection to the preparation is its cost, but it is much more palatable and convenient to carry about than the liquid acid.

In the effort to stimulate the glands of the stomach to resume their function the most efficient means at our disposal are the administration of strong meat broths as the first course of the meal, preceded by full doses of tincture of nux vomica. This drug should be pushed to its physiological limits and patients may often take 30 or 35 drops at the dose. It might be argued that nux vomica may give rise to a gastric hyperesthesia, or aggravate such a condition if it already exists. The studies of Steele,[11] confirming the previous experience of Musser, show, however, that nux vomica in full doses does not have such an effect, but relieves rather than increases the tendency to hyperesthesia of the gastric mucous membranes.

In addition to the drinking of broths, consomme, bouillon,

[10] E. H. Starling, Recent Advances in the Physiology of Digestion, Chicago, 1907, p. 85 et seq.

[11] The Relation of Excessive Gastric Acidity to Gastric Symptoms, Jour. Amer. Med. Assoc., 1906, xlvii, 496.

beef tea, etc., these patients are encouraged to have their foods well salted, in order that the chlorine supply of the body be ample for the production of hydrochloric acid. If any restriction of the dietary is indicated, undoubtedly the proteids should be the class of foodstuffs to limit in amount. With diminished peptic digestion, associated with a possibly impaired tryptic activity, proteids are certainly not well handled, and their excess in the intestine permits of undue decomposition with the production of increased amounts of indol and other cleavage products which we believe to be injurious to the organism.

Buttermilk is a specially valuable article of diet in cases of gastric anacidity, and most patients can be induced to consume three pints a day. When they tire of it, or if it is not well borne, one of the various preparations of lactic acid bacillus tablets may be given.

If the general nutrition is much impaired, associated, as is usually the case, with visceroptosis and possibly motor insufficiency of the stomach, the patient will be much benefited by assuming the recumbent position for an hour after each meal, or may be instructed to lie on the right side. Further treatment may include the wearing of an abdominal supporter, and the employment of the usual measures to combat anemia, nervous states, and other conditions which may be not only the result, but as well the contributing cause of a gastric anacidity.

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## MULTIPLE SUBCUTANEOUS HEMANGIOMAS, TOGETHER WITH MULTIPLE LIPOMAS, OCCURRING IN ENORMOUS NUMBERS IN AN OTHERWISE HEALTHY, MUSCULAR SUBJECT.

By John T. Bowen, M.D.,

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The patient was a man, aged thirty-six years, a native of Russia, who had been in this country twenty-six years. His family history was irreproachable. His father and mother were alive and well; he had four brothers who were healthy, and all of the family were living in America. None of the family had had any skin disease. He was married and had one healthy child.

He was first seen in March, 1910. He was of small stature, but exceedingly muscular. During the early part of his life and until eight years previously he had been a professional boxer of considerable reputation, and had had matches in various parts of the world. He had never sustained any serious injury. His weight

was 147 pounds. He said that he had first noticed his present affection three or four years previously, after he had given up his sporting career, and had engaged in his present occupation, that of a builder. The first lesions to make their appearance were on the back, one or two in number, and they had steadily multiplied since.

The lesions were numerous, small or moderate-sized tumors, most of them subcutaneous, so that the skin was freely movable over them. In a few instances there seemed to be a slight involvement of the corium. The surface of the skin was normal, with the exception that in a few places, not necessarily over the tumors, there was a bluish-red color from venous stasis. The distribution of these nodules and tumors was over the trunk especially. The thighs were affected, although much less prominently, and there were only a few lesions on the upper and lower arms. The head and face were completely free, and there were very few lesions upon the neck. In size the lesions varied from that of a small pea to a pigeon's egg. They were moderately firm and elastic. They were either rounded or elongated in shape, and those of medium size could in many instances be picked up between the fingers, and gave the feeling of disks or coins. The lesions were absolutely non-sensitive.

The patient was seen again nine months later, in November, 1910. The nodules had increased considerably in numbers. Some of the larger ones were now the size of a hen's egg, and their outlines could be faintly seen when the patient was examined at a distance of a few feet. A photograph of the patient would have shown only these few slight protuberances, which represented the larger lesions, the hundreds of smaller lesions which studded the trunk being subcutaneous and invisible. The patient preserved his appearance of magnificent muscular development without apparently any excess of fat tissue. The patient was positive that none of the nodules had disappeared, and he was equally certain that new ones in large numbers had appeared since last seen nine months before. There was no glandular enlargement to be detected then or at any other time. No nodules had appeared upon the head or trunk, with the exception of the tongue. During the last six months a nodule had appeared on the tip of the tongue, and it had attained the size of a bean. It was sharply elevated, only slightly excoriated, firm to the touch, and had annoyed him somewhat in eating and drinking, although it was not specially sensitive. There were no signs or symptoms in the throat. The lesion of the tongue was excised and the wound healed quickly.

The case was again examined and studied in October, 1911, and in March, 1912. The lesion of the tongue that has just been described had not reappeared and there were no abnormal appearances of the head and face. The tumors, however, especially those

FIG. 1

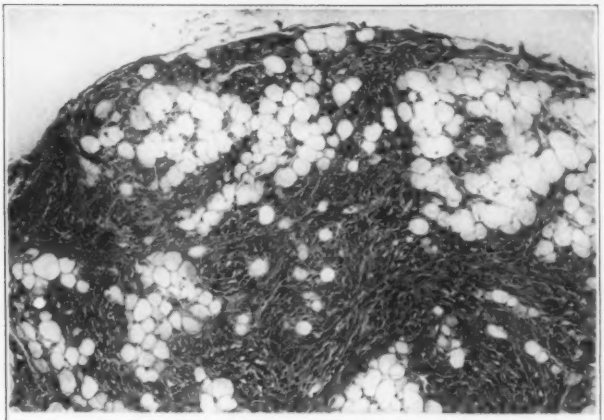

FIG. 2

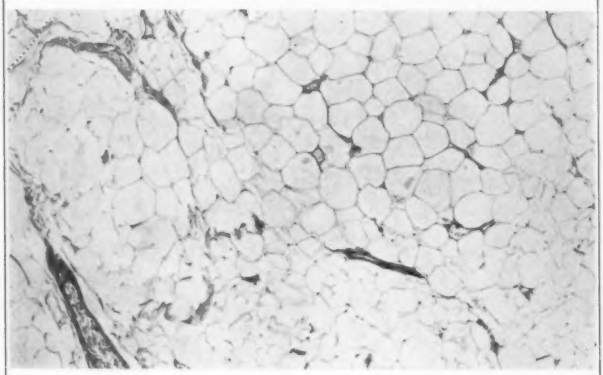

FIG. 3

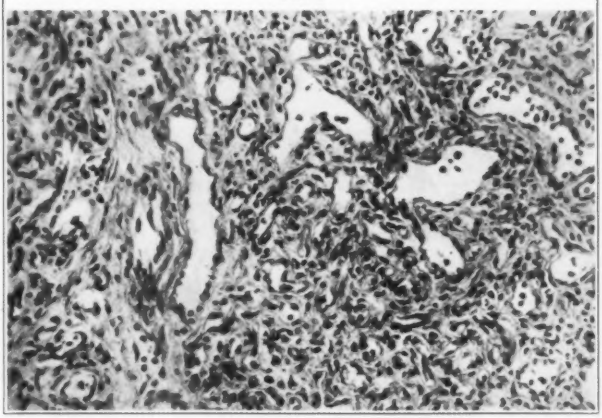

FIG. 1.—Section from one of the smaller nodules, showing growth of bloodvessels infiltrating the fat tissue.

FIG. 2.—Section from one of the larger nodules, showing pure fat tissue.

FIG. 3.—Section from the lesion of the tongue, showing a pure hemangioma.

upon the trunk, had increased greatly in numbers, and there were certain ones of larger size than before. In most places there was barely an interval of half an inch in which tumors could not be felt. Some of the larger ones, especially those upon the back and loins, had reached the size of a hen's egg, and in a few instances there were ill-defined masses, although, as a rule, the tumors were sharply bounded. The protrusion of some of the larger tumors was somewhat more pronounced, so that the appearances were slightly more evident to the eye. A few purpuric patches were present, sometimes over the lesions, sometimes not. None could be felt over the buttock, where, as indeed everywhere, he was very muscular. The largest tumor was situated on the back over the left scapular region. This tumor was somewhat elongated and less sharply defined than the majority. No lesions could be detected on the head or face, nor on the hands or feet. The thighs were moderately involved, and there were a few nodules on the lower arms and lower legs. There were no lesions on the genitals.

A careful internal examination at this time was made by Dr. J. H. Pratt, but nothing abnormal could be detected. Examination of the secretions showed no deviation from health. The patient's general health was perfect and the only symptom produced by these multitudinous growths was mental disquietude as to the final outcome.

Histological Examination. Several of the lesions of varying sizes were excised for microscopic examination. The lesions in most instances "shelled out" readily after incision of the overlying skin, and presented microscopically a yellowish appearance, similar to that of lipomas. They were resilient to the feel. Microscopically a difference was in general to be noted between the smaller or more recent, and the larger tumors. The smaller tumors, of which Fig. 1 offers a good example, were composed of a newgrowth of bloodvessels, which seemed to be infiltrating the fatty tissue in every direction within the limits of the tumor. No distinct capsule could be detected, but the tumor was sharply bounded from the normal tissue surrounding it, as was evidenced by the ease with which it was expressed after incision. In the larger nodules the amount of new-formed angiomatous tissue became much less in comparison with the fatty tissue. This gradation was very marked and constant in all the lesions excised, some half dozen in number, of varying sizes and duration of growth. The larger tumors were composed almost entirely of fatty tissue (Fig. 2), and the only difference that they exhibited from ordinary lipomas was that they might be considered somewhat more vascular. Mitotic figures were occasionally to be found in the newgrowth of bloodvessels. None could be seen in the fat tissue, but that was to be expected, considering the difficulty of such findings in ordinary lipomas.

The lesion of the tongue was totally excised. This proved to be a pure hemangioma, as shown in Fig. 3, with no fat apparent. Mitotic figures were seen in the proliferating vascular branches.

In the search of the literature that has thus far been possible no precisely similar instance has been discovered. The pronounced complication, with what must be regarded as fat hyperplasia, might call to mind the numerous cases of multiple symmetrical lipomas that have been reported from various sources in various countries. In none of these that I have seen described were the clinical appearances at all like those of the case in question. The cases of multiple lipoma present usually large masses of fat tissue in places, so that it is difficult to speak of them simply as tumors. No instance of such an extraordinary number of small tumors has been discovered among these multiple lipomas. I find a reference to an article by Berenbruch,[1] describing a peculiar case of multiple angiolipoma, but I have not been able to see the original. A remarkable case is described by Winternitz and Boggs,[2] in which there were multiple subcutaneous hemangio-endotheliomas; also the same of the intestinal tract, multiple polypi of the stomach undergoing malignant change, generalized vascular sclerosis, and cirrhosis of the liver in a mulatto, aged sixty-five years. The writers say that they could find in the literature no similar instance of multiple subcutaneous hemangio-endotheliomas. In this case the subcutaneous tumors presented a cavernous aspect.

The tendency of angiomas to infiltrate the fat tissue is well known (Borst, Ribbert). In many of these cases the growth of vessels is at the expense of the fat tissue, which gradually disappears.

In the case reported the fact that in the smaller and younger lesions the hemangiomatous element was most pronounced and that there was a gradual and progressive increase in the amount of fat tissue as the lesions became more developed, would favor the view that the growth of vessels is the primary process. The appearance of a single pure hemangioma upon the tongue where the fat tissue is normally scanty is also in accord with this theory. It seems as if the angiomatous growth invading the fat tissue causes an increase of this tissue, which in time overshadows and dominates the vascular growth, so that the larger tumors are indistinguishable from true lipomas.

[1] Ein Fall von Multiplen Angio-Lipomen combinirt mit einem Angiom des Rücken-markes, Tübingen, 1890.

[2] Johns Hopkins Hospital Bulletin, July, 1910.

# MALIGNANT DISEASE OF THE LUNG WITH SPECIAL REFERENCE TO SARCOMA.[1]

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Secondary malignant disease of the lung or pleura is not uncommon. It may arise by metastasis from distant organs or by direct extension from adjacent structures. Secondary cancer of the lung may be associated with an initial focus in one of the abdominal viscera, as the liver or pancreas; but in a larger percentage of cases it results from the extension of a primary mammary, esophageal, or thyroid carcinoma. Encephaloid or medullary cancer is the form that most frequently reaches the lung by metastasis. Secondary sarcoma of the lung most commonly originates in a primary growth in the marrow cavity of one of the long bones. The small round-cell form is most often noted.

Two autonomous formations approaching closely to both carci- and sarcoma in their morphological characteristics, and appearing in many cases as secondary growths in the lungs are the so-called hypernephroma and the malignant deciduoma. Of 22 cases of hypernephroma collected from the literature by Woolley[2] there were metastasis in the lungs in 13. Although the primary growth in these cases may correspond morphologically to carcinoma or adenocarcinoma, it not rarely affords metastasis of a purely round or small spindle cell sarcomatous type. Rolleston and Marks,[3] Woolley,[4] Adami,[5] and others emphasize this point. Malignant deciduoma, which genealogically is more closely related to carcinoma than to sarcoma, involves the lungs secondarily in nearly 50 per cent. of the cases, and in some instances is first manifested by coughing, pleuritic pain, hemoptysis, and other symptoms referable to the chest.

Primary carcinoma of the lung is rare. In the records of the Breslau Pathological Institute, out of 9246 necropsies, in which there were 1000 cases of malignant disease, Pässler,[6] found 16 cases of primary carcinoma and 4 cases of primary sarcoma of the lung. Seydel[7] among 10,829 autopsies made at the Münich Pathologic Institute found records of 1342 tumors, and of these 184, or 13.7 per cent., were in the lungs or pleura. In 83.2 per cent. the tumors were metastatic and in 16.8 per cent. the tumors were primary. Of

[1] Read before the Section on General Medicine of the College of Physicians of Philadelphia), March 25, 1912.

[2] Amer. Jour. Med. Sci., cxxv, 1903.

[3] Ibid., cxvi, 1898.

[4] Loc. cit.

[5] Principles of Pathology, i, 747.

[6] Virchow's Arch., 1896, Band cxiv, S. 191.

[7] Münch. med. Woch., 1910, lvii, No. 9.

the primary growths 11 were sarcoma of the pleura and 20 were carcinoma of the lung.

With other observers primary carcinoma has been more rare and primary sarcoma more common than the statistics indicate. Reinhard[8] found only 5 cases of primary carcinoma in 8716 necropsies. Rolleston and Trevor[9] in analyzing the post-mortem records of St. George's Hospital from January 1, 1890, to July 8, 1902, comprising 3983 cases, discovered only 8 cases of primary malignant disease of the lungs. Of these, 3 were primary sarcoma of the lung, 2 were primary sarcoma of the bronchi, and 2 were primary carcinoma of the bronchi. There was no case of primary carcinoma of the lung itself. The apparent inconsistencies in the statistics may be attributed in part to differences in nomenclature and in part also, without doubt, to the fact that some of the older writers incorrectly classified their cases. Indeed, as Mallory's[10] studies have shown, it may be very difficult or even impossible to make definite statements in regard to the cellular structure of many tumors without operative removal and immediate tissue fixation.

Primary sarcoma of the lung may spring from the lymphatic glands surrounding the bronchi, especially those in the roots of the lung, from the lymphatic vessels themselves, or from the subpleural or intrapulmonary connective tissue. Tumors developing within the lung from the connective tissue are most frequently of the spindle-cell variety, whereas those originating in the lymphatic vessels are commonly of the nature of endothelioma. Endothelioma of the pleura often invades the lung, and unless the growth is studied histologically in its entirety it may readily be mistaken for lymphosarcoma or carcinoma. As a rule, primary sarcoma is limited to one lung. It forms a large infiltrating mass, of variable consistence, and of a grayish color, often mottled with hemorrhagic areas. Metastasis, except to the mediastinal glands and tissues, are not common. In the 8 cases of primary sarcoma of the lung itself studied by Rolleston and Trevor,[11] remote metastasis were noted but once. In primary cancer, on the other hand, secondary growths are found with great frequency in the various abdominal organs, and not rarely in the muscles.[12]

The dominant symptoms of malignant disease of the lung may be those of a progressive consolidation of the lung, of stenosis of the larger bronchi or trachea, or of pleurisy with effusion. Cough and dyspnea are rarely absent. The cough varies in severity and quality, according to the size and location of the growth. It is especially marked when the larger bronchi are involved or the

[8] Quoted by Villanene, Russkij Wratsch, October 30, 1904.
[9] Brit. Med. Jour., February 14, 1903.
[10] Jour. Med. Research, 1905, viii, 113.
[11] Loc. cit.
[12] Menetrier, Art. Neoplasie, Bouchard's Patholog. Gen., vol. ii; Handford, Trans. Path. Soc., London, 1888, xxxix, 48.

mediastinum is invaded and the trachea compressed. In the latter event the cough is likely to be paroxysmal and of a ringing quality, as in aneurysm of the thoracic aorta. On the other hand, when the tumor is confined almost entirely to the vesicular structure the cough may be very slight. There is also much variation in the degree of dyspnea. When the trachea is compressed, or a large pleural effusion present, it may be intense and for a considerable period the only obtrusive symptom. Expectoration occurs in a large proportion of cases, but it may be slight or even absent. Stokes laid much stress upon the occurrence of a gelatinous reddish (currant-jelly) or brownish-black (prune-juice) sputum, evidently the result of the intimate admixture of mucus and blood; but sputum of this character also occurs in other pulmonary conditions. Occasionally, disintegration of the tumor gives rise to copious fetid expectoration resembling that of gangrene. In a number of instances the diagnosis has been made certain by the microscopic examination of tissue fragments in the sputum.

Hemoptysis, from congestion of the tissues surrounding the tumor, or erosion of fair-sized pulmonary vessels, is present in the majority of cases, and may be profuse and persistent. Pain is inconstant. It is often quite severe, however, when the pleura is involved or the thoracic nerves are compressed. Recurring attacks of pleuritic pain are not rarely the first symptom to attract attention. Enlargement of the superficial veins of the chest and localized edema sometimes result from invasion of the anterior mediastinum and occlusion of large venous trunks. More rarely, hoarseness and dysphagia arise from pressure upon the recurrent laryngeal nerve and esophagus respectively. Enlargement of the glands above the clavicle or in the arm-pit is an important symptom, but it is quite exceptional in sarcomatous cases. The temperature remains, as a rule, normal, but not infrequently in the later stages moderate fever of a remittant type supervenes and persists until the end. Cachexia sooner or later develops in most cases, and is of importance in differentiating tumor from aneurysm.

In the absence of pleural effusion, percussion usually reveals an irregular area of dulness, gradually increasing in extent. If the bronchi in the affected region are pervious, auscultation elicits bronchial breathing and broncophony. In the majority of cases, however, the bronchi are occluded, and, in consequence, both respiratory sounds and voice sounds are feeble or suppressed. When the root of the lung is involved and a main bronchus partially obstructed the respiratory sounds over a limited area may be loud and stridulous. The chest wall over the tumor is sometimes distended, but it may be retracted if there are extensive pleuritic adhesions. In tumors attaining large dimensions the heart and abdominal organs are often considerably displaced. In a case of sar-

coma of the thorax cited by Rolleston[13] the liver was so depressed that its lower border was on a level with the umbilicus.

In a large percentage of cases, symptoms of pleurisy with effusion dominate the clinical picture. If the fluid is not bloody at first, it usually becomes so after two or three tappings. Microscopic examination of the sediment sometimes affords valuable diagnostic aid. A large number of cells exhibiting numerous mitoses, especially asymmetrical division forms is in favor of malignancy (Rieder, Warthin, Dock). Rarely, secondary nodules have developed along the course of the aspiration wound.

The following cases illustrate the important features of sarcoma of the lung:

CASE I.—W. P., a male, aged twenty-four years, with a good family history. His habits had been regular and he denied venereal infection. He did not recall having had any of the ordinary diseases of childhood, with the exception of diphtheria at the age of six. After that illness he enjoyed unbroken good health until about four months before admission to the hospital, January 12, when following exposure he was seized with sharp pain in the right side of the chest. His family physician treated him for pleurisy, and in four weeks his symptoms entirely disappeared. He remained in the "best of health" until six weeks before entering the hospital. At that time he developed what seemed to be a severe cold. The symptoms were those of sore throat, with hoarseness, hacking cough, and the expectoration of frothy mucus. This condition continued unchanged for about three weeks, when he noticed one morning on arising that his face was swollen, especially over the right cheek. The swelling subsided during the day, but returned each morning. Subsequently the neck and right side of the chest also became swollen. He had slight dyspnea, but no pain, and his appetite and digestion were good. On admission the patient's condition was as follows: The face, neck, and right side of the chest were markedly edematous. The skin was pale, but the appearance was not cachectic. The tongue was slightly coated, pale, and flabby. The voice was husky; beyond slight congestion of the vocal cords, however, there was nothing abnormal in the larynx. There was slight cough at intervals, with the occasional expectoration of frothy mucus. The pupils were equal and reacted well both to light and accommodation. The eye-grounds, except for slight congestion of the retinal vessels, were normal.

The right side of the chest was nearly 4 cm. larger than the left at the level of the nipples. Respiratory movements were absent on the right side and the intercostal spaces were obliterated. The apex beat was in the sixth interspace, near the anterior axillary line, and was forcible. Vocal fremitus was entirely absent over the

[13] Diseases of the Liver, p. 19

right side, both anteriorly and posteriorly. On percussion there was flatness over the entire right side, except anteriorly above the clavicle. The cardiac dulness extended in the fifth interspace about 5 cm. to the left of the midclavicular line. On the left side there was hyperresonance. No respiratory sounds could be detected on the right side, except near the sternoclavicular articulation, where the breathing was bronchial. There were no friction sounds or rales on the right side, and vocal resonance was extremely feeble. On the left side the breath sounds were much exaggerated and scattered moist rales could be heard. A soft systolic murmur was audible at the apex of the heart, and was not transmitted. The heart sounds at the aortic area were normal. The pulmonary second sound was somewhat accentuated. The liver dulness merged above into the thoracic flatness and extended below about 5 cm. below the costal border in the midclavicular line, otherwise nothing abnormal was found in the abdomen. Neither on admission nor at any other time could enlargement of the glands in the axilla or above the clavicles be detected. The respirations were 24 to 28, and not labored; the temperature ranged between 99° and 100°; the pulses in the radial arteries were synchronous, but that on the right side was distinctly weaker than that on the left; the urine contained a trace of albumin, but no casts. Examination of the blood revealed: Hemoglobin, 65 per cent.; red blood cells, 3,872,000; white blood cells, 13,400.

January 13. The right pleural cavity was tapped at two points: first, about 3 cm. below the angle of the scapula, and then 6 cm. below the angle of the scapula, near the posterior axillary line. Each puncture brought away about 50 c.c. of bloody fluid, which soon coagulated. Much resistance was offered to the entrance of the needle, and unless the direction of the cannula was frequently changed the flow of blood would cease. The clinical diagnosis was intrathoracic growth, probably sarcomatous.

January 15. The patient's condition was not materially changed.

January 16. The physical signs were unchanged. The patient stated that his appetite was good, that he had slept well, and was very comfortable. A blood examination revealed 15,600 leukocytes, of which 68.5 per cent. were polymorphonuclears, 29 per cent. were lymphocytes, 2 per cent. were large mononuclears, and 0.5 per cent. were eosinophiles.

January 17. The patient, against orders, got up and went to the toilet at the end of the ward. Returning he fell across the bed in a state of collapse, and died within a few minutes.

*Autopsy.* Body of a well-nourished man; skin and mucous membranes pale; rigor mortis (ten hours) well marked. Heart much displaced to left side. Left pleural sac was without adhesions and free from fluid. The left lung was somewhat congested and edematous, but otherwise normal. In the right pleural sac there

were dense adhesions, with loculi containing bloody serum, the latter amounting in all to about 120 c.c. The right lung was large and firm. It weighed 2500 grams. On section it was found to be infiltrated throughout, except for a small portion of the lowest lobe posteriorly, with a dense mass of purplish gray color. A few areas of softening about the size of a pea were noted. No tuberculous foci were present. Neither the peribronchial nor the mediastinal glands were enlarged. The pericardium contained a few cubic centimeters of straw-colored fluid, and was without adhesions. The heart was slightly dilated and relaxed. It weighed 320 grams. The valves were normal. The abdominal cavity contained about 300 c.c. of clear fluid. The liver was slightly adherent to the diaphragm. It weighed 1450 grams. It was congested and apparently somewhat fatty. The spleen was congested and firm. The other abdominal organs presented no gross changes. No secondary nodules were discovered. Microscopic examination of the growth revealed a typical spindle-cell sarcoma.

Case II.—A. C., aged thirty-four years, a clerk by occupation, with a good family history. He always enjoyed good health until seven months before he came under observation, when he developed pain under his left scapula. This was shortly followed by a cough, with mucous expectoration and occasional attacks of hemoptysis. The blood was bright red in color. He sought advice in a medical dispensary and was treated for tuberculosis, but did not improve. On the contrary, his cough grew worse, his expectoration became mucopurulent and profuse, the pain continued, he developed night sweats and often felt feverish, and in three or four months lost twenty pounds.

On admission the patient weighed 118 pounds, and presented a somewhat cachectic appearance. The chest was long and flat. The left side was immobile and slightly depressed. There was no glandular enlargement. The apex beat of the heart was invisible. Tactile fremitus was marked on the right side and absent on the left side, except anteriorly above the fourth rib and posteriorly above the scapular spine. On percussion there was flatness on the left side of the chest, extending from the fifth rib anteriorly to the fourth rib in the midaxillary line, and the spine of the scapula posteriorly. Over the right lung there was hyper-resonance. On auscultation scattered dry and moist rales were heard over the right side of the chest and over the upper lobe of the left lung. On the entire right side and over the left side below the clavicle there was harsh, vesicular breathing. Over the flat area on the left side the breath sounds were scarcely audible. Examination of the heart revealed no abnormalities. The organ was apparently not displaced. The abdomen was slightly distended, but otherwise showed no changes. The temperature ranged between 97.5° F. in the morning and between 100° and 101.5° F. in the evening. The pulse was 90

to 110; the respirations were usually 24 to 30; the urine was free from albumin, casts, and sugar. An examination of the blood showed: Hemoglobin, 70 per cent.; red blood cells, 3,440,000; white blood cells, 12,400. The sputum on repeated examinations failed to show tubercle bacilli. The left pleural sac was punctured on three occasions, with negative results.

During the next four weeks there was no decided change in the general symptoms, although the patient became distinctly weaker and more emaciated. The expectoration was often blood-streaked, but only once in this period was there any marked hemoptysis. Dyspnea, which was slight at first, was now evident, especially on exertion. The fever and sweats continued as before, but there were no chills. Another examination of the blood, and the last one made, showed: Hemoglobin, 65 per cent.; red blood cells, 3,200,000; white blood cells, 14,600.

In the fifth week, during a severe paroxysm of cough, he brought up in the sputum two particles of solid matter, one about the size of a small cherry-stone, the other somewhat smaller. They were of a grayish-pink color, irregularly rounded, and firm. Upon microscopic examination these particles were found to be made up of a close aggregation of large round or slightly oval cells. The cytoplasm was abundant and the nuclei were deeply staining. There was very little interstitial reticulum. A diagnosis of intrathoracic sarcoma was now made. Three days after the expectoration of the fragments the patient was attacked with severe hemoptysis, which continued intermittently for about six hours. Following this he was much exhausted. Four days later he had another copious hemorrhage, followed by collapse, from which he never rallied. Death occurred about eight months after the appearance of the first symptom.

*Autopsy.* The body was much emaciated; the pleura on the left side presented firm adhesions below and posteriorly. On the right side there were slight adhesions posteriorly. Both pleural cavities contained a small quantity (50 c.c.) of bloody serum. The left leaf of the diaphragm was enormously thickened and tightly adherent to the left lung and spleen. The aorta, heart, and diaphragm were firmly united by adhesions. The bronchial, mediastinal, and abdominal glands were all much enlarged, but firm. The right lung was congested and edematous. On section the left lung, except at the apex, was found to be studded throughout with numerous pinkish-white nodules, varying in size from that of a pea to that of an egg. Most of these were firm, but two or three of the larger ones were almost gruel-like in consistence. The right lung was congested and edematous. It contained no nodules. The heart, apart from the adhesions surrounding it, showed no abnormalities. The peritoneal cavity contained no excess of fluid, but presented local adhesions in the neighborhood of the diaphragm, spleen, and left kidney. The right adrenal body was about the size of a small

egg, and completely replaced by a soft, reddish-white growth. The latter also extended a short distance into the superior pole of the left kidney. The right kidney, stomach, pancreas, liver, and intestines were apparently normal. No other nodules were discovered. The brain was not examined.

Microscopically the nodules in the lung presented for the most part the same picture as the fragments found in the sputum during life, although in places the resemblance to sarcoma of the alveolar type was close.

Microscopic examination of the adrenal growth showed it to be a so-called hypernephroma, some areas presenting a typically adenocarcinomatous aspect, and others exhibiting just as definitely the characters of alveolar sarcoma.

CASE III.—G. A., a Greek, aged thirty-six years, a laborer by occupation. Owing to the lack of an efficient interpretation only an imperfect history could be obtained. He had been sick for several weeks, complaining of pain in the right side of the chest, dyspnea, and cough without expectoration. During the six days that he was under observation these symptoms were still present. He was a man of medium height, decidedly pale, but not markedly emaciated. Dyspnea was very pronounced, and his lips and finger-tips were blue. The temperature throughout was normal or subnormal; the respirations were between 24 and 36; the pulse ranged between 110 and 120; the urine was somewhat scanty, but otherwise not abnormal. An examination of the blood showed: Hemoglobin, 60 per cent., red blood cells, 3,260,000; white blood cells 12,000. The physical signs were those of a pleuritic effusion on the right side. This side of the chest was immobile and appeared to be slightly distended, although the interspaces were not obliterated. Fremitus was absent and the percussion note was flat at all points below the clavicle in front and the spine of the scapula posteriorly. The breath sounds were inaudible. Over the left side of the chest there were a few scattered coarse rales, but otherwise only the usual evidences of compensatory action. The apex beat was diffuse in the fifth interspace, and slightly to the left of the midclavicular line. There were no murmurs. The lower border of the liver could be felt below the costal margin, but apart from this the results of the abdominal examination were negative. Two punctures of the right pleural sac were made on different occasions; the first yielded a few cubic centimeters of serum faintly tinged with blood, and the second, about 80 c.c. of fluid decidedly hemorrhagic. The clinical diagnosis was pleurisy with effusion, probably tuberculous. Two days after the last aspiration pulmonary edema suddenly set in and terminated fatally.

*Autopsy.* At the autopsy only the thoracic findings were of interest. The right pleural cavity contained about half a liter of bloody serous fluid. The pleural surfaces were firmly adherent over the uppermost lobe, both anteriorly and posteriorly. Below

there were no adhesions except over the diaphragm. The pleura throughout was enormously thickened and covered with numerous cartilaginous nodules. The right lung was compressed, hyperemic, and edematous. In the middle lobe there were two yellowish-white nodules, having a diameter of about 3 cm.; in the lowest lobe there were a number of nodules ranging in size from a millet seed to a hazelnut. The left pleural cavity was empty, and the left lung was hyperemic and edematous. The heart was pale and flabby, but otherwise not abnormal. The enlargement of the intrathoracic lymph glands could be detected.

Microscopically, sections of the pleura showed numerous anastamosing tubules lined with one or two layers of cubical epithelial cells, and separated by a rather dense network of connective tissue. Interspersing the latter were many round cells, with abundant cytoplasm, and deeply staining nuclei, somewhat like those in round-cell sarcoma. Microscopic examination of the nodules found in the lung revealed a wide-meshed net of delicate connective tissue, the meshes of which were filled with large round cells, having an epithelioid appearance. The cells were packed tightly in the acini, and were in immediate contact with the reticulum as in alveolar sarcoma. Many vessels were seen in the trabeculæ. The anatomical diagnosis was endothelioma of the right pleura with metastasis in the right lung.

The diagnosis of pulmonary malignant disease is often a matter of great difficulty, only to be arrived at by a careful collation of all the facts and a close observation of the progress of the case. Pulmonary tuberculosis, pleural effusion, or aneurysm, is usually suspected. Not rarely the symptoms throughout are so indefinite that the true nature of the condition may only be determined post mortem. The discovery of malignant disease elsewhere, of course, furnishes an important clue. This clue is likely to fail, however, when the growth is sarcoma and is primary in the lung. Even when the pulmonary affection is secondary the symptoms of the metastatic tumor may overshadow the entire clinical picture and the primary focus escape recognition, as in one of the cases cited above. Occasionally the examination of scraps of tissue found in the sputum furnishes conclusive evidence. In this way the diagnosis was established in Case II. Wolff,[14] Claisse,[15] Ehrlich,[16] Betshart,[17] Feldt,[18] Demorest[19] and Cornil[20] also cite instances in which the microscopic examination of tissue fragments from the sputum afforded decisive information. When pleural effusion is present, the character of the fluid, its rapid return after thoracentesis, and the cytological findings are sometimes suggestive. However, too much importance should not be attached to the occurrence of a slightly bloody exudate, since

[14] Fortsch. d. Med., Nos. 18 and 19, 1895.
[15] Lancet, March 11, 1899, p. 712.
[16] Quoted by Hampeln, Zeit. f. klin. Med., 1897, Band xxxii, H. 3 and 4.
[17] Virchow's Arch., Band cxliii, H. 1.
[18] Deutsch. med. Woch., 1903, xxix, No. 28.
[19] Med. Rec., January 16, 1904.
[20] Comp. rend. de Soc. Anat., January 27, 1905.

this is not uncommon in tuberculosis and pleurisy complicating chronic nephritis and other wasting diseases. In cases marked by consolidation of the lung, suspicion may be aroused by certain anomalies in the clinical picture, as the unusual location or distribution of the dull areas and the constant presence of blood in the sputum without tubercle bacilli. The fact must not be forgotten, however, that tuberculosis and malignant disease of the lungs not rarely coexist. Tuberculosis was present in 13 of 31 cases of malignant disease of the lung reported by Wolff[21] and in 3 of 10 cases reported by Schwalbe.[22] Hildebrand,[23] Seigert,[24] Ribbert[25] and Menetrier[26] also cite cases in which tuberculosis and malignant disease were associated in the same lung.

In any case much importance is to be attached to symptoms pointing to stenosis of the air passages, although in tumors developing within the lung these do not appear, as a rule, until the disease is far advanced, and even when such symptoms are well marked the existence of aneurysm must often be debated.

Pulmonary syphiloma may produce signs closely resembling tuberculosis on the one hand or malignant disease on the other. In the absence of any positive evidence of tuberculosis or malignant disease, a positive Wassermann reaction should be regarded as an indication for recourse to specific treatment. Echinococcic disease of the lung and dermoid cyst may yield most of the symptoms of malignant growth, although both are even more rare than the latter. Of 1816 cases of echinococcic disease occurring in the United States and collected by Sommer[27] the lung or pleura was involved in 147. Apart from the presence of cysts elsewhere, the expectoration of hydatid membrane, and the data afforded by thoracentesis, there are no characteristic signs. Presumptive evidence, however, might be forthcoming in the presence of pronounced eosinophilia and the fixation of complement in the hemolytic test. Exploratory puncture is not without danger, owing to the grave toxemia which may follow absorption of the hydatid fluid. Maydl[28] reports 11 cases of intrathoracic echinococcus disease in which a fatal result followed thoracentesis.

In the case of intrathoracic dermoid cyst the coughing up of hair is the only pathognomonic symptom. According to Shaw and Williams[29] this was observed in 7 of the 35 authentic cases reported in the literature up to 1905.

Except in rare cases the treatment of tumors of the lung or pleura can only be palliative. In the 31 cases analyzed by Seydel there were only 7 in which an operation would have offered the slightest chance of recovery.

[21] Loc. cit.
[22] Deutsch. med. Woch., 1896, xii.
[23] Virchow's Arch., 1893, Band cxxxiv.
[24] Gaz. Heb. de Méd. et de Chirurg., 1899, No. 6.
[25] New York Med. Jour., August 22, 1896.
[26] Ueber Echinokokkus der Pleura, Wien, 1891.
[27] Ziegler's Beiträge, 1888, Band ii.
[28] Deutsch. med. Woch., 1896, xi.
[29] Lancet, November 4. 1905.

# PAROXYSMAL HEMOGLOBINURIA.

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As a clinical entity, paroxysmal hemoglobinuria was first recognized and described by Dressler in 1854. In spite of the many clinical studies and the amount of experimental work on isolated cases, however, no satisfactory hypothesis was advanced to explain the pathology of this rare and curious disease until 1904, when Donath and Landsteiner[1] contributed their first paper to the subject. They attributed the attack characteristic of the disease to a specific hemolyzing substance in the blood of these patients, and they demonstrated its presence by experiments *in vitro*. Eason[2] working independently, had found this same hemolyzing substance in a case under his care. Since then a number of observations have been made by different investigators, all of whom confirm the presence of the autolysin; but with regard to the definite mode of action of this substance on red blood corpuscles there is even now no unanimity of opinion. The case here reported was studied with a view to clearing up, if possible, some of the disputed points.

History. E. P., aged thirty-eight years, porter, colored, single, was admitted to the hospital November 10, 1911.

*Family History.* Father, four brothers, and four sisters dead; cause unknown. Mother and one sister living and well. The sister resides in New York City and, so far as known, has never had an attack of hemoglobinuria.

*Personal History.* Patient was born in the West Indies, where he lived until eleven years ago, when he came to New York City. His habits are good; alcohol and tobacco in moderation.

*Previous History.* An indefinite history of a short, mild attack, called malaria, once before coming to New York. Veinereal disease denied, and no symptoms elicited suggesting an acquired infection.

*Present History.* Nine years ago, having been in New York City two years, the patient had an attack which came on suddenly in November, 1902, while he was working and apparently in excellent health. This attack consisted of a severe shaking chill, with fever, followed by the passing of black urine. In twelve hours he was as well as usual, and the urine looked normal. One week later he had a similar experience. Beginning one month later, January, 1903, he had attacks in rapid succession, and was in a hospital for ten

[1] Münch. med. Woch., 1904, li, 1590; Zeit. f. klin. Med., 1906, lviii, 173.
[2] Edinburgh Med. Jour., 1906, xix, 43; Jour. Path. and Bact., 1906–7, xi, 167.

weeks, without improvement, the paroxysms continuing at intervals throughout the summer and up to September, 1903, when they ceased spontaneously, and he was perfectly well for two years. Since September, 1905, the paroxysms have recurred at irregular intervals, for the most part in the cold season, but occasionally in summer. He found that washing his hands in cold water would induce an attack, and he says the summer attacks always followed chilling in a draught after hard work. All of the attacks since January, 1903, have been associated with severe, sharp, lancinating pain in the lumbar region, especially the right. There is also numbness and tingling of the extremities, which subsides with the attack.

*Physical Examination.* The patient is a well-built, rather small negro. He is absolutely normal, with the exception that on abdominal examination a smooth rounded mass is found in the upper quadrant on each side, taken to be the kidney, moderately enlarged, slightly movable, and not tender.

Cystoscopy: December 19, 1911, by Dr. E. L. Keyes, Jr. Bladder normal, mouths of the ureters normal, bloody urine from both ureters.

Radiograph: "Does not show calculus in either urinary tract."

Urine Examination: During an interval the urine is clear, of normal specific gravity, with no albumin. An occasional cast is found, but no pus cells and no red blood cells. During an attack the urine is dark reddish brown, containing much coagulable proteid, few leukocytes, and an occasional red blood cell. Chemical test for blood, positive.

Blood Examination: Without special reference to the attacks the blood shows: Leukocytes, 4400 to 7200; polymorphonuclears, 62 per cent. to 65 per cent.; hemoglobin (Dare), 62 per cent. to 65 per cent. (November to December, 1911), 72 per cent. (March 16, 1912).

Red blood cells, 2,700,000 (November 29, 1911), 3,600,000 (February 14, 1912), 4,800,000 (March 16, 1912). Coagulation time, eight to nine minutes (normal). Blood plates, 500,000. Malarial parasites, absent.

Wassermann Reaction: Positive, December 4, 1911.

Salvarsan: 0.5 gm., given intravenously, February 19, 1912.

Wassermann Reaction: Positive, March 25, 1912 (by Dr. L'Esperance).

Salvarsan: 0.4 gm., given intravenously, April 7, 1912.

Wassermann Reaction: Positive, April 15, 1912 (by Dr. Noguchi).

Luetin Test: Positive April 15, 1912 (by Dr. Noguchi).

Salvarsan: 0.6 gm., given intravenously, April 29, 1912.

Wasserman Reaction: Positive, May 30, 1912.

On January 5, 1912, the Ehrlich experiment was done. A tourniquet was placed about the left arm above the elbow, and the fore-

arm was immersed in ice water for five minutes. The arm was then taken out and dried, and blood was drawn from a finger into a test-tube containing a small amount of 0.8 per cent. NaCl solution. This was warmed and centrifuged. Hemolysis was present. As a control, blood was taken from a finger on the right hand, which was not immersed, before the tourniquet was removed from the left arm. This was also put in a test-tube containing a small amount of salt solution and warmed. Hemolysis was absent. During the immersion the patient complained of intense lumbar pain, with tingling of all the extremities. Within a half hour after the experiment the patient had a severe shaking chill, with rise of temperature to 102° F. The first urine voided was dark reddish brown. Urine voided three hours later was also dark brown, but the urine voided six hours after the experiment was perfectly clear amber colored.

We have then to do with a perfectly typical case of paroxysmal hemoglobinuria in a man without history and with none of the stigmata of congenital or acquired syphilis, but with a positive Wassermann reaction and positive luetin test.

The particular point of interest in this pathological condition is the hemolysin, which will be considered under the following headings: (1) Demonstration of the autohemolysin; (2) absorption of the auto-antibody from inactive serum; (3) dissociation of corpuscle antibody combination; (4) absorption of complement from active serum; (5) action of complement on red blood cells sensitized with inactive hemolytic serum; (6) mode of action of the autohemolysin; (7) etiology of paroxysmal hemoglobinuria.

The preparations used in the work here reported are designated as follows: (1) "P. Ser." The serum of the hemoglobinuric patient obtained by centrifuging defibrinated blood while still warm. (2) "P. Ex. Ser." Defibrinated blood of the same case was subjected to 0° C. for one hour, then centrifuged quickly in the cold and the serum removed. (3) "P. Ina. Ser." Some of the serum obtained in (1) was inactivated at 55° C. for twenty minutes. (4) "N. H. S." Normal human serum obtained from defibrinated blood. (5) "N. Ex. Ser." Defibrinated blood, same as (4), at 0° C. for one hour, centrifuged quickly in the cold and the serum removed. (6) "G. P. Ser." Guinea-pig serum from defibrinated blood. (7) 10 per cent. "P. Blood." From the hemoglobinuric case. (8) 10 per cent. "N. H. Blood." Normal human blood from the same case as the serum in (4). (9) 10 per cent. sensitized sheep's blood.

For these suspensions (7 to 9) 5 c.c. of the defibrinated blood were washed three times with 0.8 per cent. warm NaCl solution and made to 50 c.c., with 0.8 per cent. NaCl solution. All preparations were freshly made on the day in which the experiments were done. In every instance at least seven days had intervened since an attack. These experiments are confirmatory of a number of earlier experiments carried out on this case, in which hemolysis was shown, not only for his own but other human corpuscles. In incubating for

hemolysis it was found that after icing, if the tubes were warmed over a free flame carefully, one-half hour in the incubator was sufficient for maximum hemolysis. This technique was employed in all my cold-warm experiments.

1. Demonstration of the Autohemolysin. By subjecting oxalated blood of a hemoglobinuric patient or the serum and a corpuscle suspension of the same blood to a low temperature, then incubating at 37° C., Donath and Landsteiner obtained hemolysis "in vitro." No hemolysis took place on prolonged exposure to the cold only nor on prolonged incubation at 37° C. only. This so-called "cold-warm" experiment has given positive results in the hands of all other observers, although Meyer and Emmerich[3] were successful only thirty times in a total of sixty-nine experiments on four patients, and Kumagai and Inoue[4] were compelled to modify the original technique to get satisfactory results. In the twelve separate times that the case here reported was examined, positive results were always obtained by the original Donath-Landsteiner method.

Table I.—Demonstration of Autohemolysin.

A.

| | | Lysis. |
|---|---|---|
| 0.200 cc P. Ser. + 0.25 cc 10% P. Blood | 0° C. ½ hr. | Nearly complete |
| 0.100 cc P. Ser. + 0.25 cc 10% P. Blood | Warmed | Partial |
| 0.050 cc P. Ser. + 0.25 cc 10% P. Blood | 37° C. ½ hr. | Slight |
| 0.025 cc P. Ser. + 0.25 cc 10% P. Blood | | 0 |
| Control: 0.2 cc P. Ser. + 0.25 cc 10% P. Blood | 37° C. 1 hr. | 0 |
| Control: 0.2 cc P. Ser. + 0.25 cc 10% P. Blood | 0° C. 1 hr. | 0 |

B.

| | | Lysis. |
|---|---|---|
| 0.2000 cc P. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | | Complete |
| 0.1000 cc P. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 0° C. ½ hr. | Nearly complete |
| 0.0500 cc P. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | Warmed | Strong |
| 0.0250 cc P. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 37° C. ½ hr. | Trace |
| 0.0125 cc P. Ser. + 0.3 cc N. H. S. + 0.25 cc 10 %P. Blood | | 0 |

C.

| | | Lysis. | | Lysis. |
|---|---|---|---|---|
| 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 37° C. | 0 | Warmed | 0 |
| 0.3 cc N. H. S. + 0.25 cc 10% N. H. Blood | 1 hr. | 0 | 37° C. ½ hr. | 0 |

To demonstrate the autolysin, the experiments given in Table I were done. The results obtained show the characteristic hemolytic action with the "cold-warm" experiment, while the controls, that is, icing alone and incubating alone, are negative. Comparison of A with B shows a deficiency of complement in the "P. Ser." to completely activate all the antibody present, for the addition of complement by "N. H. S." in B shows a smaller complete lytic dose than in A and establishes 0.2 c.c. as the minimum complete lytic dose of the "P. Ser." for the amount of corpuscles used, in the presence of sufficient complement. C shows the absence of auto-

[3] Deut. Arch. f. klin. Med., 1909, xcvi, 287. [4] Deut. med. Woch., 1912, No. 8, p. 361.

lysin in "N. H. S." and the absence of an isolysin for "P. Blood," and this serum can therefore be used as complement.

2. Absorption of Antibody from Inactive Serum. Donath and Landsteiner, and Eason also, in their first papers demonstrated the hemolysin concerned in paroxysmal hemoglobinuria as an antibody-complement complex. In their later work reactivating serum was added to the inactive hemoglobinuric serum and corpuscles and hemolysis resulted with the "cold-warm" experiment. These earlier experiments do not, however, deal with the point in question. There has arisen some divergence of opinion among later workers as to the capacity of the red blood cell to absorb antibody from inactive serum on exposure to the cold. Meyer and Emmerich[5] and Hoover and Stone[6] demonstrated that such absorption could take place, but Moss[7] could not confirm their results, and concluded that "union between auto-amboceptor and corpuscle takes place only at a low temperature, in the presence of complement."

This question can best be approached by a quantitative study of the lytic action of the inactive serum before and after exposure to corpuscles in the cold. The experiments were done as follows:

*Experiment A.* "P. Ina. Ser." was titrated by mixing with 0.3 c.c. normal human serum (complement) and then 0.25 c.c. 10 per cent. "P. Blood" added—incubated at 0° C. one-half hour and then warmed and incubated at 37° C. one-half hour.

*Experiment B.* Six complete lytic amounts (0.2 c.c. equals a complete lytic dose) of "P. Ina, Ser." were iced for one-half hour, with the sediment of four times six units (0.25 c.c. equals one unit) of 10 per cent. "P. Blood"—centrifuged in the cold and the serum removed for titration, as in A, by mixing with 0.3 c.c. normal human serum and then adding 0.25 c.c. 10 per cent. "P. Blood." Incubated at 0° C. for one-half hour, warmed, incubated at 37° C. one-half hour. The results are shown in Table II.

Table II.—Absorption of Antibody from Inactive Serum.

| | In each tube 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | |
|---|---|---|
| | A.—P. ina. Ser. | B.—P. ina. Ser. after 0° C. ½ hr. with Sed. P. Blood |
| | Hemolysis after 0° C. ½ hr.—warmed—37° C. ½ hr. | |
| 0.4000 cc | Complete | Partial |
| 0.2000 cc | Complete | Slight |
| 0.1000 cc | Nearly complete | 0 |
| 0.0500 cc | Very strong | 0 |
| 0.0250 cc | Slight | |
| 0.0125 cc | 0 | |

Control: 0.4 cc P. ina. Ser. + 0.25 cc 10% P. Blood + 0° C. ½ hr. + warm + 37° C. ½ hr. = hemolysis, 0

In A the inactive serum was reactivated and gave complete hemolysis, with 0.2 c.c., the same minimum complete lytic dose as

[5] Loc. cit.

[6] Arch. Int. Med., 1908, iii, 392.

[7] Johns Hopkins Hosp. Bull., 1911, xxii, 238.

active serum plus complement, as shown in Table I—B. In B, as described here, the serum was exposed to "red blood cells" in the cold when no complement was present, as shown by the absence of hemolysis in the control. The serum was removed while still cold, and on titration, after adding complement, we find only "partial" hemolysis with 0.4 c.c. It is evident, therefore, that antibody was removed, and from the result about 85 per cent was absorbed by the corpuscles, in the absence of complement, on exposure to cold.

3. Dissociation of Corpuscle-antibody Combination. In order further to understand the behavior of the autolysin it is necessary to determine whether or not there is ever a dissociation of antibody from corpuscle on subsequent elevation of temperature after they have been united by exposure in the cold. Meyer and Emmerich state that such dissociation does occur, and they were able to remove antibody from the sensitized red blood cells by washing them with warm NaCl solution. To determine this the following tests were made:

*Experiment A.* Two and one-half complete lytic doses of the "P. Ina. Ser." were added to the sediment of ten times two and one-half units of 10 per cent. "P. Blood," iced for one-half hour, centrifuged immediately in the cold, and the serum decanted and used for titration, as shown in Table III—A.

*Experiment B.* Two and one-half complete lytic doses of "P. Ina. Ser." were added to the sediment of ten times two and one-half units of 10 per cent. "P. Blood," iced for one-half hour. It was then warmed and incubated at 37° C. for one-half hour, centrifuged, and the decanted serum titrated just as in A. The results are shown in Table III—B.

*Experiment C.* This gives the titration of the "Ina. Ser." for this day, and shows 0.4 c.cm. as the minimum complete lytic dose of this serum. See Table III—C.

Table III.

A.—Titration of P. ina. Ser. after 0° C. ½ hr. with red blood cell and decant at once.

| | | Lysis. |
|---|---|---|
| 0.4 cc decant Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 0° C. ½ hr. | Faint trace |
| 0.2 cc decant Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | Warmed | 0 |
| 0.1 cc decant Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 37° C. ½ hr. | 0 |

B.—Titration of P. ina. Ser. after 0° C. ½ hr., then 37° C. ½ hr. with red blood cell then decant.

| | | Lysis. |
|---|---|---|
| 0.40 cc decant Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | | Partial |
| 0.20 cc decant Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 0° C. ½ hr. | Slight |
| 0.10 cc decant Ser. + 0.3 cc N. H. S. + 0 25 cc 10% P. Blood | Warmed | Trace |
| 0.05 cc decant Ser. + 0.3 cc N. H. S. + 0 25 cc 10% P. Blood | 37° C. ½ hr. | Faint trace |

C.—Titration of P. ina. Ser.

| | | Lysis. |
|---|---|---|
| 0.400 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | | Complete |
| 0.200 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 0° C. ½ hr. | Very strong |
| 0.100 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | Warmed | Strong |
| 0.050 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 37° C. ½ hr. | Slight |
| 0.025 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | | 0 |
| Control: 0.4 cc P. ina. Ser. + 0.25 cc 10% P. Blood | | 0 |

In A the inactive serum was exposed to a large body of corpuscles in the cold, and the serum was removed while still cold. As we have already seen, antibody is removed from serum so treated. In this experiment, when the decanted serum is reactivated and put through the "cold-warm" test, only a faint trace of hemolysis results with 0.4 c.c., and we may, therefore, conclude that practically all the antibody has been absorbed by the corpuscles. In B the same amount of inactive serum was exposed to the same amount of corpuscles for the same length of time. It is fair to assume that the same amount of antibody was removed from the serum by the corpuscles. But this inactive serum was left with its corpuscles for one-half hour in the incubator before separating it. On decanting and titrating it just as in A we find that 0.4 c.c. gives "partial" hemolysis and 0.1 c.c. gives a "trace." We have, therefore, demonstrated that antibody is dissociated from corpuscle at body temperature, for in this experiment about 25 per cent. of that absorbed was liberated. The corpuscle-antibody combination evidently is not an absolutely stable one. The difficulty of absorbing all the antibody from the serum, no matter how great the excess of corpuscles, is shown in the experiment already given, as well as in some of those that follow. This fact would suggest that an equilibrium is established on the part of antibody between the corpuscles, whose absorptive power is greatly enhanced by the action of cold, and the serum. This has its analogy in chemistry in the behavior of two immiscible solvents toward a solute. This fact, however, does not permit of an interpretation of the behavior of antibody on a definite and purely chemical basis in contract to a biological one. That antibody would be returned in its entirety to the serum on more prolonged incubation is conceivable, but its demonstration is not essential for the purposes of discussion here.

4. Absorption of Comflement from Active Serum. Apparently biased by the well-known behavior of complement and antibody in ordinary immune sera, that is, the capacity of an antibody to unite with its antigen in the cold, while complement remains free, Donath and Landsteiner maintain the view that cold is necessary only for the union of antibody and corpuscle and that complement unites at the higher temperature, with resulting hemolysis. They have, however, no experiments bearing directly upon this point. Eason concurs with this idea, but likewise without proof. Hoover and Stone were unable to get any hemolysis unless there was an exposure of corpuscle and inactive serum to the cold after complement was added, and they first suggested that cold was necessary both for the union of complement and antibody, as well as antibody and corpuscle. Meyer and Emmerich contend that cold is not necessary for antibody complement combination. They merely state their results and give no detailed protocols of the work upon which their conclusions rest. Moss states that "the complement

does not enter into the combination, or at least not permanently, at this temperature," for he was able to demonstrate complementary action in the decanted serum after active serum was chilled with corpuscles. His work may be criticised on the ground that it was not quantitative.

Whether complement does or does not enter into combination on exposure to the cold can best be determined by a titration of complement in active serum before and after the serum is exposed to corpuscles in the cold. The experiments are given in Table IV. In

TABLE IV.

A.—Titration of Complement.

| | In each tube 0.25 cc 10% Sensitized Sheep Blood. | | | | | |
|---|---|---|---|---|---|---|
| Amount of complement | P. Ser. | P. Ex. Ser. | P. ina. Ser. | N. H. S. | N. Ex. Ser. | G. P. Ser. |
| | Hemolysis after warming and incubating at 37° C. ½ hr. | | | | | |
| 0.500000 | ..... | .. | 0 | | | |
| 0.400000 | ..... | 0 | 0 | | | |
| 0.100000 | Complete | .. | .. | Complete | Complete | |
| 0.050000 | Complete | .. | .. | Very strong | Complete | |
| 0.025000 | Partial | .. | .. | Slight | Very strong | |
| 0.012500 | Trace | .. | .. | Trace | Slight | Complete |
| 0.006250 | ..... | .. | .. | ..... | ..... | Complete |
| 0.003125 | ..... | .. | .. | ..... | ..... | Nearly complete |

B.—Titration of P. Ex. Ser.

| | | |
|---|---|---|
| 0.40 cc P. Ex. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | | Very strong |
| 0.20 cc P. Ex. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 0° C. ½ hr. | Strong |
| 0.10 cc P. Ex. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | Warmed | Slight |
| 0.05 cc P. Ex. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 37° C. ½ hr. | 0 |
| Control: 0.4 cc P. Ex. Ser. + 0.25 cc 10% P. Blood | | 0 |

Table IV—A the titrations of complement were made against 10 per cent. sensitized sheep's blood. These sheep corpuscles were sensitized by the addition of antibody in the form of inactive serum of rabbit that was immune to sheep red cells. In the first column we see that "P. Ser." that is, active serum before exposure to corpuscles in the cold, is able to act as complement, and 0.05 c.c. is enough to induce complete hemolysis. In the second column, "P. Ex, Ser." is used. This, as stated above, is serum derived from the original defibrinated blood after it was iced for one hour. 0.4 c.c. of this serum has no complementary action, and induces no hemolysis whatever. That it cannot be said that the treatment destroyed complement, a control was done with normal human serum under absolutely identical conditions, and here we see (columns 4 and 5) that the exposure to corpuscles in the cold did not decrease the complement, but actually increased it by 100 per cent. This rather interesting and curious result has been obtained with several normal sera. The titer of "G. P. Ser." is given to show the degree of sensitization of the corpuscles used. "P. Ina. Ser." was also titrated against this hemolytic system to demonstrate its complete inactivation.

It is also necessary to demonstrate that complement is absent from the "P. Ex. Ser." as far as "P. Blood" is concerned. See Table IV—B. The control shows no hemolytic action of the "P. Ex. Ser." on "P. Blood." If we add complement ("N. H. S.") hemolysis results. This shows that the "P. Ex. Ser." contains antibody, about 15 per cent. of the original amount, and lack of hemolysis in the control must be ascribed to lack of complement. Here we have conclusive proof by two methods of the disappearance of complement from active serum, that is, its absorption from active serum by exposure to corpuscles in the cold. It is shown also that this disappearance of complement takes place only from that serum ("P. Ser.") containing a specific antibody, and not from normal serum. The evidence that complement unites with antibody only under the influence of cold will be given under Section 5.

5. Action of Complement on Red Blood Cells Sensitized with Inactive Hemolytic Serum. The previous experiments show that all the complement and 85 per cent. of the antibody was removed from the "P. Ex. Ser.," and must have been taken up by the corpuscles in the cold. The proof of this last assumption will be considered later. If complement is absorbed at one and the same time with antibody, can it or can it not unite with antibody subsequent to the union of the latter with corpuscles. And if it can unite subsequently, does this union take place in the warm or only under the influence of cold? The fact that complement is absorbed in the cold, which is quite contrary to the usual behavior of complement in immune sera, would certainly suggest that it must do so to act at all. The following experiments were done to determine the action of complement on corpuscles previously sensitized by exposure in ice to inactive hemolytic serum.

*Experiment A.* Four times two doses of the "P. Ina. Ser." (1.6 c.c.) and four units of 10 per cent. "P. Blood" (1 c.c.) at 0° C. one-half hour, centrifuged in the cold, decant the serum, and wash the corpuscles once with ice cold 0.8 per cent NaCl solution and suspend in 1 c.c. (original volume) of cold salt solution. These corpuscles, kept cold, were then used to titrate the "P. Ina, Ser." after it had been complemented with "N. H. S." The results are shown in Table V. The results obtained in the titration of the "P. Ina, Ser.." against unsensitized cells (Table II—A) are reproduced for comparison.

*Experiment B.* In this case a larger proportion of "P. Ina. Ser." was added and left in the cold for a longer period of time with corpuscles to sensitize them, if possible, more strongly. They were then used as in Experiment A: Five times four doses of "P. Ina. Ser." and five units of 10 per cent. "P. Blood" were put at 0° C. for one hour, centrifuged in the cold, washed once with ice-cold salt solution, and the corpuscles suspended in the original volume (1.25 c.c.) of ice-cold salt solution. The titration with these strongly sensitized cells is shown in Table V—B.

TABLE V.

A.—Titration of P. ina. Ser. using Mod. Sensitized 10% P. Blood.

| | | Lysis | Tab. II–A |
|---|---|---|---|
| 0.40 cc P.ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | | Strong | Complete |
| 0.20 cc P.ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | 0°C. ½ hr. | Strong | Complete |
| 0.10 cc P.ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | Warmed | Partial | Complete |
| 0.05 cc P.ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | 37°C. ½ hr. | Slight | Strong |

B.—Titration of P. ina. Ser. using Strongly Sens. 10% P. Blood.

| | | Lysis. |
|---|---|---|
| 0.40 cc P.ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | 0°C. ½ hr. | Trace |
| 0.20 cc P.ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | Warmed | Trace |
| 0.10 cc P.ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | 37°C. ½ hr. | Trace |
| 0.05 cc P ina.Ser.+0.3 cc N.H.S.+0.25 cc 10% Sens.P.Blood | | Trace |

In this experiment we have a demonstration of a very curious inhibiting action. That this is not due to any substance originally present in the inactive serum is evidenced by the fact that in Experiment II—A this same serum in combination with complement gave active hemolysis. The result must be due in some way to the condition of the red blood cells as a result of their previous treatment, and there are three possible hypotheses upon which it may be explained: (1) That complement must unite with antibody at the same time that antibody unites with corpuscle; (2) deflection of complement; (3) complementoid inhibition.

To determine which of these explanations suffices, the following experiments were done:

*Experiment A.* This gives the titration of the "P. Ina. Ser." for this day.

*Experiment B.* Five times four doses of "P. Ina. Ser." (0.2 c.c. equals one dose) plus five units of 10 per cent. "P. Blood," iced for one hour, centrifuged, serum decanted, and the corpuscles washed once with ice-cold salt solution and suspended in the original volume (1.25 c.c.) of ice-cold salt solution. The corpuscle suspensions were divided into five tubes, 0.25 c.c. to each tube, the first four kept ice-cold and treated as shown in Table VI—B. The fifth tube was carefully warmed over a free flame; complement was then added and the tube kept at 37° C. for one hour.

TABLE VI.

A.—Titration of P. ina. Ser.

| | | Lysis. |
|---|---|---|
| 0.40 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | | Complete |
| 0.20 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 0° C. ½ hr. | Complete |
| 0.10 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | Warmed | Nearly comp. |
| 0.05 cc P. ina. Ser. + 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 37° C. ½ hr. | Very strong |
| 0.04 cc P. ina. Ser. .. .. .. + 0.25 cc 10% P. Blood | | 0 |
| 0.3 cc N. H. S. + 0.25 cc 10% P. Blood | 37° C. 1 hr. | 0 |

B.—Titration of P. ina. Ser. using Sensitized P. Blood.

| | | Lysis. |
|---|---|---|
| 0.4 cc P. ina. Ser. + 0.3 cc N.H.S. + 0.25 cc 10% Sens. P. Blood | 0° C. ½ hr. | Very strong |
| 0.2 cc P. ina. Ser. + 0.3 cc N.H.S. + 0.25 cc 10% Sens. P. Blood | Warmed | Very strong |
| 0.1 cc P. ina. Ser. + 0.3 cc N.H.S. + 0.25 cc 10% Sens. P. Blood | 37° C. ½ hr. | Very strong |
| 0.3 cc N.H.S. + 0.25 cc 10% Sens. P. Blood | | Very strong |
| 0.3 cc N.H.S. + 0.25 cc 10% Sens. P. Blood | 37° C. 1 hr. | 0 |

In this case, as in the former, there is definite inhibition of hemolysis, as shown by comparison of A with B, for with the sensitized corpuscles twice the complete lytic dose only gives "very strong" lysis. These corpuscles, as did those in V—B, all give the same amount of lysis irrespective of the amount of inactive serum added, and this is the case even in the fourth tube, where complement alone was added. Our first hypothesis them nust be discarded, for we have demonstrated by this fourth tube that complement can attach itself to antibody after antibody has been attached to corpuscle; but B—5 shows further that this union can take place only under the influence of cold, as already stated by Hoover and Stone, for if, after icing, tubes are carefully and quickly warmed over a free flame and complement added, as done here, the results are uniformly negative. This cannot be attributed to separation of antibody, for it has already been shown that this is rather reluctantly given off from the corpuscle on warming. Secondly, there is no ground for an explanation on the basis of "deflection of complement," so-called, for the less antibody added the less deflection possible, and the amount of hemolysis would be in inverse proportion to the amount of antibody added. This is not the case. The third hypothesis—compelmentoid inhibition—is an extremely interesting one. At the present day serologists, generally speaking, agree with Ehrlich's original conception that complement is composed of two fractions: the "endstück," or toxic part, which in hemolysis produces the lytic action, and a "mittelstück," by which the toxic portion is joined to the antibody. The "endstück" is thermolabile, and, therefore, absent in inactive serum, while the "mittelstück" is thermostable, and present in inactive serum. It has already been shown in this paper that the complement in serum of paroxysmal hemoglobinuria unites with antibody on exposure to corpuscle in the cold. There is, therefore, every reason to believe that complementoid will attach itself to antibody, and corpuscles when exposed to inactive serum take up antibody and antibody takes up complementoid in so far as this happens to be present, and will, therefore, block complement. That some hemolysis took place in the experiments can be attributed to the fact that all the antibody was not completely saturated with complementoid, for in none of the experiments on the serum of this case was there enough complement to completely activate all the antibody present. The question of complementoid in this serum has been studied further by a series of experiments, the protocols and discussion of which are reserved for a later paper; suffice it to say here that the presence of complementoid is shown.

6. Mode of Action of the Autohemolysin. To review briefly then we have seen that antibody is taken up from inactive serum in the cold, that is, is absorbed in the absence of complement; that this combination is not absolutely stable, for a certain amount is

dissociated on elevation of temperature; we have also seen that complement is absorbed from active serum, together with antibody, in the cold, that complement unites with antibody only under the influence of cold, and finally, that the red blood cells exposed to inactive serum in the cold are more or less resistant to hemolysis on account of the complementoid present in inactive serum, the degree of resistance depending on the amount of complementoid present. These facts warrant the following statement as to the mode of action of the hemolysin: Antibody unites with corpuscle and complement unites with antibody only under the influence of cold, the lytic action being manifested on subsequent elevation of temperature. They cannot unite in any other way.

In order further to sustain this theory, we must be able to interpret the result of various experiments by it.

*Experiment* 1. One complete lytic dose (0.2 c.c.) of "P. Ina. Ser." plus 0.25 c.c. 10 per cent. "P. Blood," iced for one-half hour. Centrifuged in the cold and save "decant" serum for the next experiment. The corpuscles were suspended in 0.45 c.c. of cold 0.8 per cent. NaCl solution and 0.3 c.c. "N. H. S." added and incubated at 0° C. for one-half hour, warmed, then incubated at 37° C. for one-half hour. Result, hemolysis slight.

*Experiment* 2. The "decant" serum was added to the sediment of 0.25 c.c. 10 per cent. "P. Blood," with 0.3 c.c. "N. H. S.," iced for one-half hour, incubated at 37° C. for one-half hour. Result, hemolysis trace.

In the first experiment one complete lytic dose does not give complete hemolysis; there is evident inhibition, and this can now be explained on the basis of "Komplementoid Verstopfung." In the second experiment there was very little antibody present in the "decant" serum, but in the presence of complement, icing with untreated corpuscles gave slight hemolysis.

If corpuscles do take up antibody and complement in the cold, it should be possible to demonstrate this action also. For this purpose I have repeated one of Moss' experiments, using the exact proportion given by him and practically the same technique:

*Experiment.* 1 c.c. "P. Ser." (active) and 0.1 c.c. "P. Corp.," containing as little salt solution as possible, were iced for one-half hour, centrifuged in the cold, and corpuscles washed twice with salt solution at 0° C. They were suspended in 0.75 c.c. salt solution and incubated at 37° C. for one-half hour. Result, hemolysis slight. Complement added (0.25 c.c., "N. H. S.") and temperature maintained at 37° C. for two hours. No increase of hemolysis. Incubated at 0° C. one-half hour, then 37° C. for two hours. No apparent increase of hemolysis.

The result obtained here is different than that given by Moss, who found hemolysis after the addition of complement and without exposure to the cold. In my experiment hemolysis showed after

incubating the washed cells, and must have been due to anchored antibody and complement. This is the first positive result of this sort recorded, and it has been possible to duplicate it, although not constantly. The demonstrated dissociability of antibody and complement may be the explanation, although I am inclined to attribute it to the dissociation of complement, either "end-piece" or "mid-piece" from the combination, for it is readily conceivable that prolonged washing of corpuscles even with ice-cold salt solution might liberate end-piece or mid-piece of complement from corpuscle antibody combination. Experiments to determine this point have not been done. Hemolysis in this experiment was slight only, but if we analyze this it is found that we have but two and one-half complete lytic doses of serum (0.4 c.c. "P. Ser." was the minimum complete lytic dose on this day) added to the sediment of eight units of corpuscles. Naturally they are not highly sensitized and no greater hemolytic effect could be expected.

Meyer and Emmerich[8] give an experiment in which a tourniquet was placed about the finger of a hemoglobinuric, and it was immersed in ice water ten nimutes. The blood then taken from the finger was centrifuged and the serum decanted. They do not state whether the corpuscles were washed or not. To the corpuscles was added normal human or guinea-pig serum, and without any further cooling, but merely on incubation, hemolysis resulted. They give this as an example of the union of complement to antibody in the warm, but there is no ground for their conclusion, for the result can be explained on the supposition that complement, as well as antibody, was already bound to the corpuscle "*in vivo*," and the complement added took no part in the reaction. The same result might have been obtained merely on the addition of salt solution without any complement. They do not state, however, that any such control was done.

It has not been possible to explain all of the varying results of experiments found in the literature on any one basis. It is a well-known fact that in cases where the paroxysms have been frequent the "cold-warm" experiment *in vitro* is very apt to be negative. In such cases we may presume a deficiency or absence of complement, and Meyer and Emmerich have shown that such did occur in some of their cases. Even in normal serum it has been frequently shown that there is considerable variation in the complement content from day to day. That absence of antibody occurs seems less likely on account of the difficulty of absorbing all of it even from defibrinated blood, but a deficiency might occur temporarily, although we know nothing as to the rapidity of its formation. That anti-complementary substances can and do occur is well known and Kumagai and Inoue appear to have demonstrated their presence in paroxysmal hemoglobinuria in a number of their cases.

[8] Loc. cit.

Such a formation could well account for the apparently spontaneous cures that take place from time to time in the course of this disease. Such a remission is shown in the history of this case. No such substance was present, however, during the period of observation. The negative and anomalous results so frequently obtained in test tube experiments with inactive serum are, however, explainable on the ground of complementoid inhibition. To reactivate inactive serum, complement should be added to it and mixed before corpuscles are added. By this technique positive results can be obtained which might otherwise be negative.

7. Etiology of Paroxysmal Hemoglobinuria. In spite of the work that has been done on paroxysmal hemoglobinuria the basic etiologic factor is still a matter of speculation. Considering the fact that we are apparently dealing with a true autolysin, our general knowledge of the production of such bodies certainly suggests that it may be the result of the rapid and extensive disintegration of homologous or autogenous red blood corpuscles within the body. In the first place, then, concealed and internal hemorrhage would seem to offer the proper predisposing factor. This aspect of the subject was reviewed by Eason in his second paper. Traumatic hemoglobinurias are on record, but while such hemorrhages are common, a resulting hemoglobinuria is extremely rare, is merely temporary and unlike the disease under discussion, in that cold is not a factor in the production of the hemoglobinuria.

Then, again, malaria is a condition that fulfils all the theoretical requirements for the production of a lysin. The conception of hemoglobinuric fever as a malarial manifestation is very earnestly disputed at the present time; in fact, the trend of opinion among authorities on tropical medicine is rather strongly in favor of its independent origin, but even were we to consider hemoglobinuric fever as a malarial manifestation, it would still be impossible to regard malaria as in any way etiologically related to paroxysmal hemoglobinuria, for on clinical grounds they are absolute antitheses as far as the mortality and the relation of climate to attacks is concerned. Moreover, a malarial history is very infrequently elicited in paroxysmal hemoglobinuria, and in spite of very careful experimental search, Barratt and Yorke[9] were not able to demonstrate an autolysin in the serum of cases of malaria or hemoglobinuric fever.

Finally, animal experimentation has been resorted to in an attempt to demonstrate the production of autohemolytic antibodies under ideal conditions. Ehrlich and Morgenroth[10] first studied this subject. They were unable to induce the formation of an autolysin in goats, experimentally, by the intraperitoneal injection of the laked blood of other goats, although an active isolysin developed.

[9] Ann. Trop. Med. and Hyg., 1909, iii, 152, Series T. M.
[10] Berl. klin. Woch., 1900, No. 21, p. 1 and 11.

They did not try the effect of cold on uniting any hypothetical auto-antibody to the red blood corpuscles. They argue that as the injection of an isolysin causes the production of anti-isolysin, so would the production of an autolysin lead to the formation of its antibody, but no such body could be demonstrated. That such an antibody need not develop, however, is abundantly proved by the fact that none has been demonstrated in the serum of hemoglobinurics in spite of the presence of the autolysin. Fejes and Kentzler[11] did succeed in one case of four when they injected rabbits, first with aleuronat solution intraperitoneally, and on the next day injected intraperitoneally 7 c.c. of autogenous blood plus the complete lytic dose of goose serum for this amount of blood. They state that the serum from one rabbit showed a hemolysin that behaved in all respects like that of paroxysmal hemoglobinuria in test tube experiments, but hemoglobin never appeared in the urine when the animal was chilled.

One fact that is particularly prominent is the association of syphilis, either congenital or acquired. Clinical observation of itself is quite impressive. Stempel (1902), quoted by Eason, found 30 per cent. positive in 77 cases in the literature. Of Kumagai and Inoue's 20 cases, 85 per cent. are given as luetic.

With the introduction of the Wassermann reaction these percentages have been still further increased. Of 37 cases now in the literature, including my own, on which the Wassermann reaction is reported, 33 or 90 per cent. are positive. It is, however, essential to bear in mind that this reaction is not specific; that is, is not dependent upon syphilitic antibodies for the complement absorption. This is evidenced by its occurrence in the serum of a large percentage of normal rabbits and in human serum just before and after death, irrespective of cause, by its high percentage in frambesia, leprosy, relapsing fever, and malaria, and particularly by the fact recently reported by Noguchi, but still unpublished, that complement binding rarely took place when he used as antigen his pure culture of treponema pallidum, although the Wassermann reaction, done simultaneously, was positive.

It was in view of these facts that the luetin test was done in the case here reported. Noguchi[12] found his reaction positive in 96 per cent. of 23 hereditary cases and absent in all of 146 controls. As stated above, the reaction was positive in this case. It is, however, too new to warrant our placing absolute dependence upon it at this time.

That syphilitic infection does seem to bear definite relation is further shown by the investigation of Donath and Landsteiner. They examined the serum of 65 cases of general paresis *in vitro* for

[11] Zeit. f. klin. Med., lxxi, Heft 3 to 6, p. 194.
[12] Jour. Exp. Med., 1911, xiv, No. 6.

an autolysin, and found it present in 6 cases, two of which gave very marked reaction and 4 but slight. Using the 2 severe cases, the Ehrlich experiment, by icing a finger, showed hemolysis, but they were not able to induce an attack of hemoglobinuria in either. In 195 other cases of infectious and systemic disease, newgrowths and intoxications, including 28 cases of "lues," they were not able to show the presence of any hemolysin in the serum by their test tube experiments. They were led to suggest that the presence of the hemolysin in the serum is not sufficient of itself to induce the urinary manifestations of the disease and that vasomotor disturbances might be important contributing factors favoring the necessary temperature depression in the exposed tissues. Kumagai and Inoue have also recently reported such examinations for an autohemolysin. Thirty cases that were non-syphilitic by history and Wassermann reaction showed no lysin present. Their 13 cases of secondary syphilis also showed no lysin. Of 35 cases of tertiary and metasyphilitic disease 7 showed the presence of a hemolyzing substance. The Ehrlich experiment was performed on 4 of these, and 1 case gave a typical manifestation of paroxysmal hemoglobinuria. The other 3 responded by an attack which these authors consider a mild form of the disease; that is, albuminuria and urobilinogenuria with typical temperature and leukocyte changes but no hemoglobinuria.

We have, however, at our command one further and perhaps crucial test by which to determine the syphilitic or non-syphilitic nature of this disease, and that is the therapeutic test. Of the older writers, cited by Eason, Murri (1885) reports 2 cases and Kopp (1885) 1 case cured by inunctions of mercury. One of Moss' cases received "salvarsan," and while the Wassermann reaction was still positive at the end of four months, the attacks seemed to be beneficially influenced, although the autolysin was still present in the serum. Strange to say, of all the recent cases in literature not one has been followed to its definite and logical conclusion in this regard; that is, no observations have been made on any case in which, as a result of treatment with mercury and iodide and salvarsan, the Wassermann reaction has become negative. My own case still has a strongly positive reaction four weeks after the third injection of "salvarsan." I hope to be able to report observations later after the Wassermann has become negative.

SUMMARY. The observations here reported are based upon experiments with the blood of a typical case of paroxysmal hemoglobinuria.

The serum contains a complex hemolysin capable of dissolving the red blood corpuscles of the individual himself or other individuals by means of the cold-warm experiment. Positive results were obtained in all of the twelve examinations made at different times.

Auto-antibody is absorbed from serum in the absence of com-

plement, and on elevation of temperature is more or less completely but slowly dissociated.

Complement is absorbed from active serum on exposure to corpuscle in the cold. It will join with antibody after the latter has united with corpuscle, but this union takes place solely under the influence of cold.

Corpuscles sensitized with inactive serum show but slight hemolysis on the addition of complement as a result of complementoid inhibition.

As a result of clinical observation, the Wassermann reaction, the luetin test, and the serological studies in metasyphilitic disease, it seems safe to say that syphilis is the most important, possibly the only, etiologic factor in paroxysmal hemoglobinuria, but there are as yet no observations on the presence or absence of the hemolysin after the disappearance of the Wassermann reaction as a result of syphilitic treatment.

## A CASE OF DELAYED DEVELOPMENT IN A BOY TREATED WITH THYMUS GLAND.[1]

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The physiology of the thymus gland is very imperfectly understood. No one of the ductless glands appears to have a more active part in the economy, especially in the younger years of life, and yet its complete removal is not accompanied by those striking manifestations which follow removal of the thyroid or adrenal. It cannot be concluded, however, that because the removal of a gland is not followed by an acute death, it plays no important part in nutrition. The evidence afforded by removal of the sexual glands is proof on this point.

The laboratory investigations are not altogether in accord. Certain points, however, seem to be fairly well established. The thymus remains in an active condition during the presexual life of an animal, but with the onset of sexual maturity it undergoes a retrogression which finally amounts to an almost complete atrophy. The involution of the thymus appears to be a more rapid process when the sexual glands become mature. When castration is performed before puberty the thymus does not show the same degree

[1] Read before the American Pediatric Society, Hot Springs, Va., May 30, 1912.

of involution found in normal animals. Some observations point to the belief that thymectomy in guinea-pigs is followed by an earlier ripening of the sexual glands, while other experiments with chickens show that thymectomized birds have much smaller sexual glands than the controls. There appears to be an intimate relation between thymus and sex glands in respect to their mutual development and also with respect to the effect on nutrition.

The second point in which there seems to be some agreement in the experiments is in the relation of thymus removal to the development of the skeleton. While thymectomy is not followed by an acute death, the animals subjected to the operation do not in many cases grow to the same size, have the strength, or show the resistance to infection exhibited by controls. In respect to the bones, they are of a smaller size, are softer, and the epiphyseal line is broader and more irregular compared with controls.

These conclusions seem to have a fairly definite relation to the results obtained in the treatment of the case about to be described.

There has been no active substance found in the thymus which compares with adrenalin or iodothyrin. For therapeutic purposes the whole gland, either fresh or dried, has been administered in most instances. Until thymus implantation is perfected or until the active principle is discovered, such a method seems the only one available.

In February, 1910, a mother referred by Dr. Brooks Wells brought her son, aged sixteen years and four months, to consult one of us (Kerley) regarding what she termed "a failure of development." She stated that the boy had made no perceptible growth in over two years, that his genitals were small and undeveloped, and that the testicles were not in the scrotum. She was greatly worried, fearing that the boy would never be a man. Her statement further was to the effect that the boy was mentally sound, was active in play, and normal in mentality, as proved by his standing in school. He was in classes corresponding to other boys of his age.

Examination showed the boy to be delicate in appearance, normal in all respects excepting that he was undersized, his height being 56 inches and his weight 76 pounds stripped, both weight and height being about that of a boy, aged eleven to twelve years.

The penis was small and shrunken, the testicles were very small, and although there was no retention and they could readily be brought into the scrotum, they rested in the canal a greater part of the time. There had never been an erection of the penis, and there was neither pubic hair nor hair in the axilla.

The treatment instituted was that of lightening the school work, more hours in bed, and a suitable diet. Tincture nucis vomici, arsenic, and cod-liver oil comprised the medication. The patient was seen at about one month intervals during the following nine months. At this time there was a gain of 3 pounds in weight.

His height was the same and there was no change whatsoever in the sexual development. The family were extremely troubled and requested that every effort be used in the boy's interest. At the suggestion of Dr. Beebe, all medication was discontinued and desiccated thymus extract, 15 grains daily, was prescribed.

During the first six months of thymus administration the genitals, penis, and testicles perceptibly enlarged, and after nine months' use the first erection occurred when aged seventeen years and ten months. This was new and novel and amused the patient very much. At the completion of one year of treatment, when aged eighteen years, hair appeared on the pubis and in the axilla. He had gained 1 inch during the year, standing 57 inches, and had gained 11 pounds, weighing 87 pounds.

During the next six months, which brings us to April of this year, 1912, when aged eighteen years and six months, he had gained 2 inches in height, bringing him at the present time to 59 inches in height, and gained $8\frac{1}{4}$ pounds in weight, increasing the weight to $95\frac{1}{4}$ pounds. The testicles have remained in the scrotum during the last six months. The voice changed in February of this year, when he was aged eighteen years and four months.

In the eighteen months under treatment there was a gain of 3 inches in height after he was aged seventeen years, and $19\frac{1}{4}$ pounds in weight when there had been no growth according to the mother's statement for two years and nine months before.

The sexual organs are apparently normal and well developed. The use of the thymus might be considered a coincident in a case of retarded development; such cases of late development, however, are most unusual. No claims are made for the thymus. We appreciate that one case proves but little.

Six other cases of slow growth or retarded development are under observation with thymus at the present time. These cases will be reported later and will help to establish the point that naturally will arise in the mind of the reader whether or no thymus was operative in the case reported or whether it is to be looked upon as a coincident, and that the phenomena we observed would have taken place without its use.

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## ACUTE PANCREATITIS.[1]

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The following case is so suggestive, and presents so much that is typical of acute pancreatitis, that its history is given first:

[1] Read in abstract before the Southern California Medical Society, December 6, 1911.

CASE I.—F. J. C., male, aged thirty-six years, married, a native of Minnesota, by occupation a foreman in a stone cutting establishment, 5 feet 8 inches tall, weighing 210 pounds, was taken sick August 8, 1910. His family history was negative. He himself had had measles, mumps, chickenpox, and, when aged nine years, "bilious remitting fever," with which he was sick three months, and from which he fully recovered. He had never suffered from any venereal diseases, nor did he use tobacco. Once in ten days or two weeks he consumed large quantities of beer while playing cards, but did not become intoxicated. He was always a hearty eater. He had never suffered from any symptoms of stomach or gall-bladder disease. August 7 he had slight chest pains and a little discomfort in the epigastric region, which he attributed to "taking cold." He went to work as usual on August 8, feeling better, but at 10 A.M. was taken with an agonizing, cutting, tearing pain in the epigastric region. Upon being given a drink of whisky his pain was increased, and was also felt in the back, being most marked in the lower dorsal and upper lumbar region to the right of the spine. This excruciating pain, in spite of many doses of morphine hypodermically, continued for about a week. It was accompanied by continual vomiting of greenish material. He had but few symptoms of collapse, although the pulse became rapid. He had moderate fever after the first day. For three days he had obstinate constipation which did not yield to any form of treatment. High enemas were expelled without fecal matter, but he passed a little flatus. On the fourth day the adminstration of a half ounce of castor oil caused his bowels to move several times.

After a week he still had much pain in the back, but none in the abdomen. Laparotomy had been positively declined. The patient came under personal observation August 19. He was found resting easily, without febrile temperature, the pulse 90, full and regular. He did not have pain, neither was he vomiting. He was slightly jaundiced. The heart and lungs were negative. The abdomen was somewhat rigid. The liver edge, sharp and regular, was felt about two and one-half inches below the costal margin. It was not enlarged upward, nor was it tender. The spleen could not be palpated. In the median line, just below the margin of the liver, and insensibly shading into it, midway between the xiphoid and umbilicus an indefinite mass was felt, which was rather tender. No continuation of this mass could be traced either to the right or left. There was no special muscle rigidity or tenderness over McBurney's point. The bowels were somewhat constipated, and the stools were "putty colored." The urine was rather scanty, and contained bile, but did not contain albumin or sugar. There were no casts. Examination of blood showed: Hemoglobin (Dare), 80 per cent.; erythrocytes, 4,500,000; leukocytes, 12,000, of which a differential count gave polymorphonuclears, 70 per cent; lymphocytes, 22 per

cent; large mononuclears and transitionals 6 per cent; eosinophiles, 2 per cent.

He gradually improved and insisted on going about, visiting my office two or three times, the first occasion being on September 8. At this time the liver was still enlarged, but the mass in the median line was not palpable, and the jaundice had disappeared. He did not feel well, however, had a little tenderness in his abdomen, a temperature of 99° F., and did not regain his appetite or strength.

On September 15 he had a second attack, with fever, vomiting, rapid pulse, slight jaundice, clay colored stools, etc., but without pain. He developed a slight cyanosis, which persisted throughout the remainder of his illness. The mass was again palpable, being more easily felt than in the earlier part of his illness. He showed some improvement by September 20, losing his temperature and rapid pulse. Laparotomy was urged, but firmly declined, as was all operative interference throughout his illness, although frequently advised. On September 26 his temperature, which had been subnormal for two or three days, again rose, with the physical signs of pleurisy in the left chest.

Form this time until his death on October 27 his fever was remittent, usually ranging from 98° to 99° F. in the morning to a maximum of 102° to 104° F. in the afternoon. Sweats were frequent. His pulse was continuously above 100, averaging about 115. It was regular. The respirations varied from 22 to 30, and were often irregular, and accompanied by dyspnea. The urine was scant, never containing any albumin, but always showed an increased amount of indican, and also contained bile. Sugar was not present until about a week before his death, and then only a trace, and was not constant. The jaundice, although slight, was persistent. Emesis was a constant symptom, and one of the most pronounced throughout his sickness. He usually did not vomit his food, particularly solid food. The vomitus was fluid, olive green or greenish brown in color, of a very offensive odor, and the amount often so large that it seemed to exceed the patient's fluid intake, as high as twenty-eight ounces being expelled at one time.

During the last two weeks of his illness, the vomitus was often dark brown and fetid, proving on chemical examination to contain altered blood.

More or less tympanites were constantly present; belching and the passage of flatus from the bowels were also frequent. The bowels were never more than slightly constipated. The feces were sometimes dark brown and well formed, occasionally liquid, and occasionally the typical stool of obstructive jaundice. They were not fatty.

On October 21 the patient had a violent chill, with a sudden rise in temperature to 104.4° F. and a pulse rate of 160, followed by collapse, with rectal temperature of 96. 2° F. From this he rallied

and two days later his stool was exceptionally offensive, with much pus, and full of a material closely resembling sand in consistency and color. From this time on the stool contained a varying amount of a liquid or semiliquid slate-gray substance,with metallic luster and offensive odor, often containing shreds of tissue. On October 27 the patient had four hemorrhages from the bowels in the course of a few hours, three of them profuse and bright red in color, but not clotted when passed. After this he rapidly sank, and in a few hours died.

An autopsy was performed by Dr. Stanley P. Black fifteen hours after death. There was much fat necrosis in the omentum, mesentery, and the peripancreatic fat. The liver was enlarged and fatty. The gall-bladder was filled with altered bile, which was, however, readily emptied into the bowel. One small calculus was found in the neck of the gall-bladder, but the ducts were patulous. The spleen was enlarged to twice its normal size, and contained a wedge-shaped anemic infarct. The foramen of Winslow was closed and the lesser omental sac was converted into an abscess cavity, in which lay the pancreas, so broken down that scarcely a vestige of normal pancreatic tissue remained. A perforation about 0.5 cm. in diameter was present in the transverse colon; this communicated with the lesser omental cavity, and fresh clots were adherent to its edges. The heart showed slight fatty infiltration. A plastic pleurisy was present on both sides, but more marked on the left. Otherwise the organs were normal.

Acute pancreatitis occurs usually in adults, aged from twenty to fifty years. It is about twice as frequent in males as in females. It is more often seen in fat, strong individuals than in the thin or feeble, and possibly a little oftener in those addicted to the use of liquor. A careful reading of the reported cases leads one to the conclusion that many of the patients had one or more previous attacks of acute pancreatitis from which they recovered, the symptoms being wrongly ascribed to the gall-bladder or stomach and duodenum. This is not to be wondered at in view of the fact that about half of the cases of pancreatitis are accompained by gallstones. Only when a more severe attack occurred for which an operation was performed, or in which death resulted, with an autopsy, was the true diagnosis of pancreatitis made.

Opie[2] has pointed out and emphasized the close relationship between acute pancreatitis and cholelithiasis, and has laid great stress upon the effects of stone in the common duct obstructing or occluding the ampulla of Vater, thus converting the bile duct and the duct of Wirsung into a common tube, and so permitting the gall-bladder to force bile into the duct of Wirsung. It has been proved experimentally by Flexner[3] and others that bile will produce

[2] Diseases of the Pancreas, 1910, second edition.
[3] Jour. Exper. Med., 1906, viii, 167 to 177.

necrosis of the pancreas. It had also been proved experimentally that the injection of even small quantities of duodenal contents into the pancreatic duct will cause necrosis of the pancreas. Invasion from this source might be expected to be most common; but the results of bacteriological examination in cases of pancreatitis have not been uniform, and the mucous membrane of the ampulla of Vater is so arranged that, in the dead body at least, it has not been found possible to force material from the duodenum past it. Moreover, the necrotic parenchyma may contain no organisms, the products of inflammation being found only at its margins, and then only after the lapse of an appreciable interval of time after the onset of the trouble.

Williams and Busch,[4] however, have performed experiments on animals which make it seem probable that some cases of acute pancreatitis may be caused by the regurgitation of duodenal contents into the diverticulum of Vater, the previous passage of gall-stones having dilated the opening in the papilla, and thus rendered the diverticulum more patent than in health. Futhermore, in about one individual in ten the duct of Santorini is the larger, and affords an outlet for the secretion of the greater part of the pancreas. The opening of the duct of Santorini is not as well guarded as is the diverticulum of Vater, and when this anomaly of the duct exists the entrance of duodenal contents through it may explain some cases of acute pancreatitis. Infections by direct extension through the wall of the intestine and also through the medium of the blood stream or lymphatic channels have also been suggested as possible causes of pancreatic inflammation, but no clinical data have been brought forward to support these hypotheses.

Injuries in the upper abdomen, although occasionally causing pancreatic hemorrhage, give rise to an inconsiderable portion of the cases under discussion. Mumps gives rise to a certain number of cases of acute pancreatitis by metastasis; about 10 per cent. in Egdahl's[5] collective investigation. Such cases are usually mild, eventuating in recovery. On the whole it cannot be said that we have as yet accurate knowledge of the etiology of the condition.

The initial symptom, occasionally after a day or two of gastric uneasiness, is usually agonizing, almost unbearable pain felt in the upper abdominal or lower thoracic region, exceptionally in the lower abdomen or about the appendix, and occasionally referred to the back, in the lower dorsal region. It may be paroxysmal or continuous, but its distinguishing characteristic is its great severity. It has been explained on the ground that it was caused by the stretching of the parietal peritoneum. This pain is soon accompanied by nausea and vomiting of a greenish watery fluid. Belching

[4] Trans. Assoc. Amer. Phys., xxii, 304 to 314.
[5] Johns Hopkins Hosp. Bull., 1907, No. 193, 130 to 135.

is also usually present, and is often persistent throughout the attack. Obstinate hiccough occasionally occurs.

At the onset the temperature is normal or subnormal and the pulse is slow and full, but the pulse becomes rapid early in the attack. Symptoms of collapse soon appear, with rapid, weak, thready pulse and subnormal temperature. While collapse usually occurs early it may be delayed for a day or two, or be absent altogether. This condition of shock is apt to be prolonged. If the patient survives, these symptoms are usually succeeded by fever of a moderate degree, although occasionally the disease pursues its entire course without any elevation of temperature. The pulse remains rapid in a majority of cases, and the pain with nausea and vomiting continues. Cyanosis, particularly of the face, is often a well-marked symptom. In about 25 per cent. of the cases a slight jaundice appears. In about 50 per cent. an obstinate constipation is present, in which the bowels cannot be moved by any agent. Usually a little flatus is passed, particularly if high enemas are given. In three to five days the bowels move spontaneously or under the influence of some mild cathartic, such as castor oil. The abdomen is somewhat tympanitic, rather tender all over, and especially so in the epigastrium, a little to the right of the median line. One may sometimes feel an indefinite mass halfway between the xiphoid and umbilicus. It is rarely possible to palpate the acutely inflamed pancreas, and a mass is felt only after a collection of fluid occurs in the lesser omental cavity, therefore this sign is of little value for early diagnosis.

The mind usually remains clear throughout the disease. Blood-good,[6] however, in speaking of the second stage of pancreatitis, says: "In addition to fever and leukocytosis there is usually a delirium which we seldom see in other abdominal abscesses. In the 3 cases which I have observed the delirium has impressed me as a characteristic sign. The delirium may be described as that observed in typhoid infection."

Death, which may occur in the first few hours, most frequently occurs between the second and fourth day. If the patient survives, in about a week the violent symptoms abate, and while the belching, nausea, and vomiting are apt to be persistent, diarrhea or only moderate constipation succeed to what appeared at first like intestinal obstruction; the temperature is lower; the pulse fuller; the jaundice may disappear; the pain is gone; and only epigastric tenderness remains. Occasionally, as in the case here reported, and in one reported by Dick,[7] the patient may seem convalescent, and a free interval supervenes before the stage of pancreatic abscess. Or, indeed, he may recover, as occurs in possibly one-fourth of the cases.

[6] Internat. Clinics, 14th series, i, 264. [7] Edinburgh Med. Jour., 1910, v, 3, 217 to 234.

In a majority the symptoms only diminish somewhat in intensity, and after ten days or two weeks the fever often becomes irregular in type, sometimes accompanied by chills, the vomiting and belching still persist, sweating occurs, especially at night, the mass is more readily felt, and occasionally the whole site of the pancreas may be outlined by palpation. Percussion over the mass gives flat tympany, due to the interposition of the stomach. Infective conditions, as pleurisy or pericarditis, may now appear, and hemorrhage from the stomach or bowel may be added to the picture.

The urine presents no special characteristics. Febrile albuminuria and a few hyaline or granular casts are usually present. Sugar is rarely found, as glycosuria does not occur so long as only a small portion of the gland functionates, which is usually the case. Indican is sometimes present. Lipase, a fat-splitting ferment, is occasionally found in the urine, which is strong presumptive evidence that the pancreatic fat-splitting ferment is present in the peritoneal cavity, from which source it is being extracted by the urine.

The reaction of Cammidge,[8] about which so much has lately been written, does not seem to be so successful in the hands of others as in those of the author. Cammidge says: "My experience with the improved method has been most satisfactory, for in every case where pancreatitis has been found to be present, the urine has given more or less marked reaction, corresponding to the extent of the lesions. Normal urines have given no reaction, and control cases . . where there was no pancreatic lesion, have also proved negative."

In careful studies recently reported by Wilson,[9] Kinney,[10] Whipple,[11] and others little value is accorded to the test. Wilson, reporting on 504 tests from Mayo's clinic, says: "The end results, judged by Mr. Cammidge's own criteria, must be considered as a means of diagnosticating disease of the pancreas, as both valueless and misleading. There is no apparent clinical relationship between disease of the pancreas and any of our various types of end reaction."

Kinney, reporting from Dr. Deaver's service in the German Hospital, Philadelphia, says: "Very little dependence can be put upon a negative reaction, and a positive reaction can only be considered of value as a confirmatory examination."

The blood usually shows an early but comparatively slight increase in leukocytes, without any great relative increase of the polymorphonuclear variety; this is to be expected, the condition being toxic rather than infective. Later, after gangrene and infection have taken place, a typical polymorphonuclear leuko-

[8] Surg., Gyn., and Obstet., 1906, iii, 3, 440 to 444.
[9] Ibid., 1910, xi, 2, 156 to 159.
[10] Amer. Jour. Med. Sci., 1910, No. 6, cxl, 878 to 883.
[11] Johns Hopkins Hosp. Bull., 1910, No. 236, xxi, 339 to 352.

cytosis may appear. In protracted cases anemia of the secondary type is common.

The stools are but rarely fatty; they may or may not present the appearance of obstructive jaundice, depending upon the amount of obstruction of the common duct, due either to gallstones or pressure of the enlarged head of the pancreas. In perforation of the bowel hemorrhage may occur, and pus is found in the stools. In a few instances a necrotic slough of the pancreas has been passed from the bowels, as first observed by Chiari,[12] in 1862, the patient being well seventeen years later.

Not all cases follow this regular type, especially in the mode of onset they may vary from the rule. Some have little pain, only a sense of epigastric uneasiness; in others, fever is entirely absent for quite a time; occasionally, nausea is not pronounced; and collapse may not occur. Some, indeed, present at the onset only the symptoms of one of the continued fevers. The following case illustrates pancreatitis of gradual onset:

Case II.—Mr. J. H. H., married, aged fifty-five years, a native of Michigan, travelling salesman by occupation, became ill early in August, 1905. He had a slight afternoon temperature and some nausea, but no vomiting. His abdomen was a little tender, and he had slight constipation. After about a week with these symptoms he took to his bed. When first seen on August 14 he was found with a temperature of 102° F., a slow, full, dicrotic pulse of 70, without nausea, somewhat constipated, with a little tympanites, and abdominal tenderness. The urine contained a trace of albumin and a few granular and hyaline casts, but was otherwise normal. A provisional diagnosis of typhoid fever was made, but after a day or two this had to be abandoned, for while the pulse and temperature curve were like those of typhoid, the spleen was not palpable, no rose spots appeared, the Widal test was negative, and above all the leukocyte count was 16,000, with the polymorphonuclears predominating. About August 21 the patient began to have nausea again, and had occasional vomiting of a greenish fluid. He also had for the first time a sensation of weight in the epigastrium, which directed particular attention to that region. The abdomen was not now rigid nor distended, and after a couple of days, although the patient was stout, with a fat abdomen, a sense of epigastric resistance was noticed. This developed so that by the fourteenth day of illness an indefinite mass, corresponding exactly to the location of the pancreas, could be mapped out. Pain became more pronounced, and vomiting more frequent, changing from green to blackish brown. The pulse also increased in rate and became feebler, sweats occurred, and the temperature assumed more of the septic type. A diagnosis of acute

[12] Wien. med. Woch., 1876, p. 292; 1880, xxx, 139.

pancreatitis was made, and operation was advised. The abdomen was opened through a median incision by Dr. George W. Lasher, on September 4, who found fat necrosis and a necrotic pancreas, which was drained. The patient did not rally, and died September 6.

Autopsy by Dr. Stanley P. Black about fourteen hours after death revealed a pancreas every part of which was necrotic. Fat necrosis was present in the abdominal fat, and the gall-bladder was filled with altered bile and "sand." The intestines showed no evidence of typhoid fever.

Cases of this kind, as pointed out by Bloodgood, seem to pass through the stages of hemorrhage and necrosis symptomless, the patient not feeling ill until secondary bacterial infection occurs.

The morbid anatomy varies with the duration of the disease. In some cases death occurs suddenly, and nothing is found except hemorrhage into and about the gland, with little evidence of inflammation. Such cases have been designated pancreatic apoplexy, or pancreatic hemorrhage.

In others dying within the first few days the gland is usually found enlarged and firm, and with necrotic areas dark red or reddish black in color. The whole organ is seldom involved, and sharply defined areas of normal tissue are present. All of the structures of the pancreas, the parenchyma, interstitial tissue, and blood-vessels are alike implicated in the necrosis.

Hemorrhage into the organ is so constant a feature as to have given the disease at this stage the name of acute hemorrhagic pancreatitis.

Much discussion has arisen as to whether the necrosis precedes or follows the hemorrhage, but the most widely accepted view seems to be that the necrosis of the vessels sets free the blood.

The hemorrhage varies much in its amount and extent, sometimes being scarcely noticeable, and at other times the whole lesser omental bursa is distended, and blood oozes through the foramen of Winslow. The peripancreatic tissues are also often infiltrated with blood, and a blood-stained fluid is practically always present in the peritoneal cavity.

The products of acute inflammation are not constant or widespread, and are found usually only at the margins of the necrotic masses. Indeed, it is generally believed that bacteria if present have no etiological relationship to the lesion, but are secondary invaders.

Gradually the pancreas into which hemorrhage has taken place becomes necrotic, shading off from a chocolate color to a slate-gray, forming a foul-smelling mass, in which the pancreas may be wholly spacellated, and to which the term acute gangrenous pancreatitis has been given. With the invasion of bacteria suppuration takes place. Adhesions close the foramen of Winslow, and there is an accumulation of fluid in the lesser peritoneal cavity. This may

erode the retroperitoneal tissue, and the pus burrows down into the left lumbar region; or perforation through the diaphragm, or into the stomach, duodenum, or transverse colon may occur. Portions of the necrotic pancreas may be discharged by the bowel, as previously noted.

In some cases multiple abscesses or only one or two large abscesses are found, without any evidence of hemorrhage or gangrene; or suppuration may be diffuse throughout the gland; or abscess of the lesser peritoneal cavity may be present. Owing to their anatomical characteristics these cases are usually classed by themselves as acute suppurative pancreatitis. Clinically, however, no such distinction can be made, for while in many of them the onset is gradual, the symptoms are less severe, and they tend to run a chronic course; in others, as in the case reported by Cheney,[13] they have exactly the same symptomatology as the acute hemorrhagic form.

In all but the suppurative conditions Opie prefers the term "hemorrhagic necrosis of the pancreas" as more nearly describing the pathological changes.

Fat necrosis, a conspicuous feature of the disease, is always present to a greater or less extent. It was first described by Balser[14] in 1882, while Fitz,[15] in the greatest contribution ever made to this subject, first pointed out the relation between it and pancreatitis. It is usually limited to the fat of the abdominal cavity, the areas being most numerous and often coalescent in the region of the pancreas, with discrete foci in the omentum, mesentery, and perinephritic fat. Areas have also been observed in the subcutaneous fat, and in the subpleural and pericardial fat. These, however, are rare. The spots vary from one to several millimeters in diameter, often surrounded by a narrow zone of cell proliferation, and with their opaque tallow-like appearance, present a sharp contrast to the noraml fat about them. When small and numerous they have been mistaken for tubercles.

Langerhans[16] showed that fat necrosis was caused by the splitting of fat into fatty acids and glycerin, the fatty acids being deposited within the cell and the glycerin absorbed. The fatty acids later combine with calcium salts.

This necrosis, as has been abundantly proved by numerous experiments, is caused by the setting free of the pancreatic secretion with its fat-splitting enzyme, directly into the tissues, and is, as Opie has said: "A consequence of pancreatic disease, and bears much the same relation to lesions of the pancreas as does jaundice to hepatic disease. Its presence gives evidence that the pancreatic secretion has been diverted from its normal channels into the interstitial tissue of the organ and into neighboring organs."

[13] Jour. Amer. Med. Assoc., 1909, lii, 1819 and 1820.
[14] Virchow's Archiv, 1882, xc, 520.
[15] Boston Med. and Surg. Jour., cxx, Nos. 8, 9, and 10.
[16] Virchow's Archiv, 1890, cxxii, 252.

While this condition is occasionally found with other pancreatic lesions, in them it is not abundantly distributed, and is only constant with hemorrhagic or gangrenous pancreatitis. It is, as Fitz pointed out, much less frequently associated with suppurative lesions.

In the event of recovery these areas of fat necrosis may entirely disappear by a process of absorption, with a proliferation of the fixed connective-tissue cells.

The diagnosis of acute pancreatitis is not easy, and is usually made with certainty only at operation or autopsy. Fitz,[17] who gave the first accurate description of the symptoms, said, in speaking of the diagnosis: "The symptoms are essentially those of a peritonitis beginning in the epigastrium and occurring suddenly, during ordinary health, without obvious cause. The diagnosis, therefore, is based on pain, tenderness, and tympany limited to the region of the pancreas, and on the gradual development of a deep-seated peritonitis in the same place. The differential diagnosis lies, practically, between an irritant poison, perforation of the digestive or biliary tract, and acute intestinal obstruction.

In perforations of the hollow viscera, the tenderness and rigidity are much more marked, but the pain is not so agonizing, nor are pain and collapse so prolonged as in acute pancreatitis.

In intestinal obstruction, also, the severe constitutional symptoms are not present early to any such degree, and abdominal palpation excites colicky pains, while in pancreatitis the absence of indican from the urine, the decreased intestinal peristalsis, the greater intensity of pain, and the passage of flatus from the bowel are valuable indications.

Acute pancreatitis has also been mistaken for fulminating appendicitis, but in that condition the pain is more apt to be about or below the umbilicus, with a considerable rise of temperature, and the signs of a beginning general peritonitis appear early.

Biliary colic may simulate acute pancreatitis, especially as many cases are preceded by typical biliary attacks; but in pancreatis the greater severity and long continuance of pain, the wider diffusion of the pain, the collapse so frequently present, and the appearance later of an indefinite tumor mass in the epigastrium should put the physician on guard, and cause acute pancreatitis to be considered; moreover, in suppurative cholangitis, the pain often radiates to the right subscapular region, and tenderness and muscle spasm are greater in the right upper quadrant.

Ptomain poisoning may be suggested by the early symptoms, but it is to be remembered that this condition is usually attended by diarrhea from the beginning, which is a rare condition in the first days of an acute pancreatitis.

The prognosis is bad. Fully 60 per cent. of recognized cases die.

[17] Loc. cit.

Many succumb to the disease from the second to the sixth day, the third being the day of greatest fatality. It is now a well-established fact that trypsin poisoning is responsible for the death of those cases which do not go on to gangrene. The intensity of the poisoning depends on the amount of the gland destroyed by the necrosis; this explains the varying degrees of toxicity, from that which kills in a few hours to that seen in mild cases which eventuate in recovery.

The prolonged shock is also ascribed to this same toxic agent. Some investigators have attributed the early deaths, particularly those occurring within the first twenty-four hours, to a reflex from the sympathetic ganglia near the pancreas, analogous to death caused by a blow over the solar plexus.

Cases caused by or accompanied by gallstones seem to have a less favorable outcome than those in which they are not present. In Egdahl's[18] collective investigation of 105 cases, 30 cases out of 44 with gallstones died, while only 17 out of 32 cases not complicated by stone ended fatally.

Women seem to have a better prognosis than men. Less often attacked, they seem, when ill with this disease, to have more resistance, and a smaller percentage succumb during the hemorrhagic stage.

The suppurative forms are liable to become somewhat chronic and, with efficient drainage, may get well. Undoubtedly many cases recover which, owing to the difficulty of diagnosis, have been ascribed to other causes.

The treatment is surgical. Aside from symptomatic treatment, all that avails is free drainage. A few cases, possibly one-fourth, recover without surgical treatment.

In mild doubtful cases gastric lavage and rectal alimentation put the stomach and duodenum at rest, and so favor the reduction of inflammation and swelling of the ducts, and thus, by reëstablishing drainage through the common duct, favor recovery.

The intense pain requires repeated injections of morphine, and the collapse may be combated by normal saline injections. Strychnine and diffusible stimulants are also of value. The intestinal distention, if excessive, may be relieved by high rectal injections. Cathartics are useless for the obstinate constipation of the first few days.

Much discussion has arisen as to whether these cases should be operated on early. Fitz, in his original article, disapproved of it, saying of laparotomy: "An operation which, in the early stages of this disease, is extremely hazardous."

Guleke,[19] however, has virtually proved that the cause of death is the trypsin intoxication, and this being the case, a laparotomy

[18] Loc. cit.

[19] Archiv f. klin. Chir., 1908, lxxxv, 615 to 662.

done as early as the condition of the patient warrants, permits the escape of a considerable quantity of peritoneal fluid which contains this ferment.

In a good many cases, as in Case II, reported by Dick,[20] recovery occurred after an early exploratory laparotomy, in which a few ounces of bloodstained fluid escaped and fat necrosis was observed; but the pancreas was not disturbed, and the abdomen was closed without drainage. How much good an operation of this extent may do is problematical. Drainage is always indicated, as it still further empties the peritoneal cavity, and tends to limit further necrosis of the pancreas. Some operators have made incisions into the gland, but the great tendency to hemorrhage from this organ and the difficulty of controlling it must not be forgotten. Ransohoff[21] has reported a case in which death evidently took place from hemorrhage, although the gland itself was not incised. The gall-bladder and ducts should be investigated and calculi removed, but the condition of the patient is usually such in these early operations that this procedure must be deferred to a later date. The extent of operation is still a moot question, and must depend largely on the patient's condition.

With the formation of pancreatic abscess the indication for extensive drainage is clear, and the earlier this is performed, before the patient is exhausted and septic, the better the prognosis. Even then a large percentage die. When it is remembered, however, that without drainage death is inevitable the duty of the physician is plain. In those cases in which an abscess can be made out in the region of the left kidney it may be reached through a lumbar incision, but in all other cases the abdominal route, with drainage through the gastrohepatic or possibly through the gastrocolic omentum would seem preferable, because of the greater accessibility and opportunity for more careful exploration.

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## THE EFFECT OF COLD AIR UPON THE CIRCULATION IN HEALTHY AND SICK INDIVIDUALS.[1]

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The following observations were carried out at the House of Relief to determine whether in cold air we possess an agent of any therapeutic efficiency for combating the vasomotor and cardiac

[20] Loc. cit. [21] Ann. Surg., 1910, xli, 5, 670 to 681.

[1] Read before the Section in Medicine of the New York Academy of Medicine, February 20, 1912.

weakness which so often complicate infectious diseases and post-operative conditions, and the treatment of which by drugs is so unsatisfactory.

Preliminary experiments were conducted on 9 adults, who were either convalescent from operations or suffering from indifferent medical conditions like constipation, but whose circulations were apparently normal. They were in bed at least twelve hours before any observations were made. Systolic pressures were then taken in a warm room, every ten or fifteen minutes for an hour or longer, until the individual readings differed but slightly. Then the bed containing the patient was rolled from the warm room to the roof ward, which is open on three sides to the air. Each patient was well covered with blankets and a skull-cap, so that only the face was exposed. Blood-pressure readings were then made by the auscultatory method every five or ten minutes, by the same person, using a Stanton sphygmomanometer.

The following table summarizes our results:

| Name. | Age. | Average systolic blood pressure in warm room. | Maximum blood pressure out-of-doors. | Maximum blood pressure attained in | Duration increased blood pressure. | Length of exposure. | Temp. out-of-doors. |
|---|---|---|---|---|---|---|---|
| S. | 34 | 108 | 115 | 15 minutes | 30 minutes | 4 hours | 21° F. |
| F. | 45 | 120 | 145 | 30 minutes | 4 hours | 4 hours | 22 |
| .... | .. | 118 | 118 | .... | .... | 45 minutes | 38 |
| .... | .. | 111 | 146 | 3 hours | 6 hours | 8 hours | 14 |
| W. | 18 | 104 | 108 | 20 minutes | 40 minutes | 1 hour | 22 |
| .... | .. | 98 | 108 | 5 minutes | 5 hours | 12 hours | 18 |
| S. | 45 | 107 | 124 | 15 minutes | 2 hours | 8 hours | 44 |
| .... | .. | 105 | 110 | 15 minutes | 1 hour | 8 hours | 25 |
| G. | 16 | 100 | 108 | 10 minutes | 25 minutes | 1 hour | 22 |
| R. | 19 | 114 | 114 | .... | .... | 8 hours | 14 |
| D. | 46 | 122 | 132 | 3 minutes | 30 minutes | 1 hour | 22 |
| K. | 17 | 108 | 118 | 2 hours | 6 hours | 8 hours | 14 |
| H. | 31 | 120 | 124 | 8 minutes | 30 minutes | 1 hour | 30 |

Average blood pressure before exposure, 110; average blood pressure after exposure 120.

Eleven of the 13 experiments showed a rise of blood pressure varying between 4 and 35 millimeters of mercury, the average increase being equivalent to 10 millimeters. The maximum pressures were reached in from three minutes to three hours, persisted for varying lengths of time, and were often succeeded by a fall to the initial levels before the exposure had terminated. This is not a marked effect, for we found that 5 of these same men when kept quietly in bed in the ward showed an average daily variation of blood pressure amounting to 15 millimeters. Only the fact that in a majority of cases the rise occurred after a few minutes of exposure enabled us to attribute it to the cold air. It might be surmised that these initial rises were due to psychic or accidental causes rather than to the cold air. Had this been so the effect would have been transient, instead of persisting as it did. The pulse rate

showed approximately no change. The diastolic pressures also varied but slightly, in the several cases in which they were read.

Van Oordt[2] has carried out somewhat similar experiments, exposing his patients, however, entirely uncovered to a temperature averaging 44° F., for periods varying between five and thirty min-

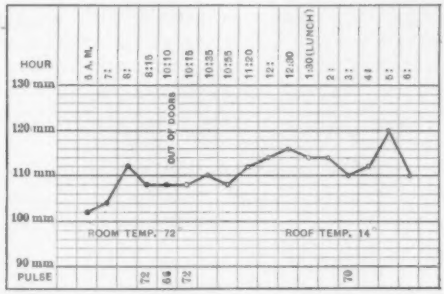


CHART 1.—Blood pressure reaction in normal individual with face exposed to cold air. Portions between circles represent observations made out-of-doors.

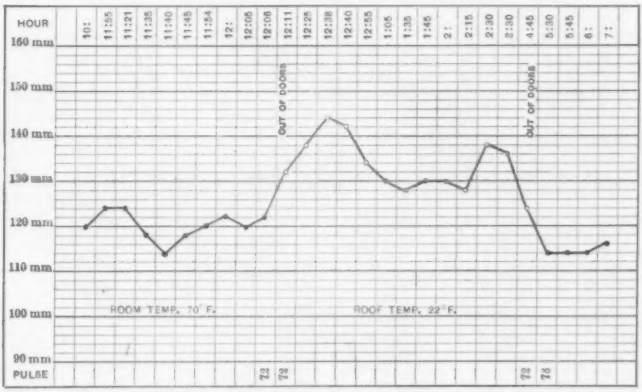


CHART 2.—This chart shows by far the most marked and consistent reaction we obtained The patient was a Chinese, suffering from constipation. A temperature of 38° produced no reaction, one of 22° a marked reaction (represented above), and one of 14° F. a still more marked and persistent rise.

utes. In 5 normal adults he noted an average rise of systolic blood pressure equivalent to 12 millimeters of mercury. This is but slightly more than the rise in our men, who were, with the exception of the face, entirely covered; that is, stimulation of the nasal mucosa by air at a temperature varying between 14° and 23° F, caused about the same pressor effect in our subjects (presumably through

[2] Zeit. f. Diät. und physikal Therapie., ix, 1905–06, S. 338.

reflex action on the vasomotor centre) as was caused in Van Oordt's subjects, by exposure of the entire body to a temperature of 44° F.

Under the same conditions as obtained in the experiments on normal men, observations were then made in various forms of disease.

The following table summarizes our results with cases of lobar pneumonia. All of the men were actively sick, running high temperatures:

| Name. | Age. | Day of disease. | Average syst. blood pressure in warm room. | Maximum syst. blood pressure out-of-doors. | Time exposed. | Temperature out-of-doors. |
|---|---|---|---|---|---|---|
| C. | 31 | 3 | 125 | 126 | 8 hours | 23° F. |
| O. | 26 | 3 | 103 | 98 | 1 hour | 23 |
| O. C. | 21 | 7 | 112 | 112 | 8 hours | 23 |
| E. | 24 | 5 | 123 | 121 | 8 hours | 35 |
| S. | 54 | 8 | 140 | 142 | 9 hours | 18 |

The results were quite negative. There was no constant effect on the pulse.

We have observations on but 1 case of typhoid fever, in a man, aged twenty-seven years. The blood pressures were very low, varying between 60 and 100 almost from the first week.

| | Ward. | Out-of-doors. | Ward. | Out-of-doors. |
|---|---|---|---|---|
| Day of disease . . . . . | 32–38 | 38–44 | 44–46 | 46–48 |
| Temperature . . . . . | 99°–102° | 99°–101.6° | 99°–102° | normal 48th day |
| Average systolic blood pressure . | 78 | 104 | 102 | 115 |
| Average pulse rate . . . . . | 85 | 95 | 104 | 80 |
| Temperature of air . . . . . | 68° | 52°–50° | 68° | 42°–50° |

It seems as if in this one case the out-of-doors treatment had a favorable effect on the blood pressure.

The following are the results in 2 cases of tuberculosis running high temperatures, 1 case of serofibrinous pleurisy, with moderate fever, and 1 case of cardiac insufficiency from chronic myocarditis.

| Name. | Age. | Disease. | Average systolic blood pressure in warm room. | Maximum systolic blood pressure out-of-doors. | Maximum pressure attained in | Time of exposure. | Temp. out-of-doors. |
|---|---|---|---|---|---|---|---|
| Y. | 31 | Acute pneumonic phthisis | 108<br>112 | 109<br>122 | ....<br>7 hours | 8 hours<br>8 hours | 33° F.<br>13 |
| M. | 36 | Tuberculous pleurisy | 102<br>92 | 108<br>110 | 30 minutes<br>13 hours | 7 hours<br>8 hours | 33<br>10 |
| C. | 25 | Sero. fib. pleurisy | 98 | 105 | 8 hours | 8 hours | 34 |
| M. | 44 | Chronic myocarditis | 150 | 148 | .... | 8 hours | 25 |

The fourth experiment is the only unquestionably positive one. There was no constant effect on the pulse in these cases.

Our attempts to influence the pulse or blood pressure being thus without result in practically all except one of our sick cases, it seemed worth while, in view of Van Oordt's experience, to see whether a greater exposure of our patients would have any positive effects. Accordingly, comparisons were made between the patient's condition when out-of-doors and warmly covered and when out-of-doors and covered with only a sheet. The time of exposure varied between thirty and thirty-five minutes. Cases with moderately high fever were selected, and as soon as the patient complained of feeling chilly the experiment was stopped.

The following table shows our results:

| Name. | Diagnosis. | Average blood pressure before exposure. | Temp. immediately before exposure. | Max. blood pressure during exposure. | Temp. after exposure. | Difference in pulse. | Temp. of air. |
|---|---|---|---|---|---|---|---|
| S. | Pneumonia | 108 | 103.0° | 134 | 102.0° | None | 38° F. |
| G. | Pneumonia | 109 | 103.0 | 108 | 101.8 | 96–92 | 38 |
| Y. | Acute pneumonic phthisis | 138 | 102.8 | 142 | 102.0 | 110–108 | 38 |
| | | 110 | 103.2 | 110 | 102.0 | 104–102 | 20 |
| | | 118 | .... | 120 | | | |

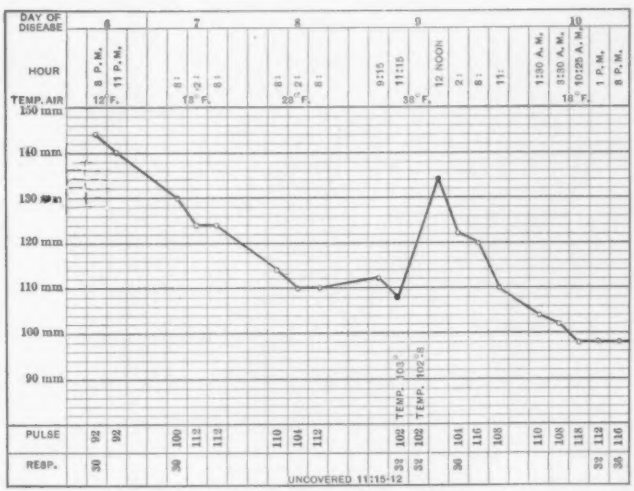


CHART 3.—Effect upon the blood pressure of a patient with pneumonia and delirium tremens when out-of-doors and covered and when only covered with a sheet.

The pulse was slowed and the temperature lowered in four experiments. The blood pressure was not markedly affected except in 1

case, a chart of which is given above. The patient was suffering from pneumonia and delirium tremens, but was quiet for some hours at the time of the experiment.

The summary of our results in the cold-air treatment of various infections shows that of 16 experiments carried out on 12 patients but 2 were positive, judging from the time of onset and degree of the rise in blood pressure. The heart was slowed in 4 of the experiments, in which the patient was covered with only a sheet. No sweeping conclusions can be drawn from an experience with so few cases, but the generally negative results make it seem improbable that the therapeutic value of cold air in diseases of adults is due to any dynamic effect on the circulation. That cold fresh air is of the utmost value in the treatment of infectious diseases is unquestionable, but its *modus operandi* must be sought in other directions.

CONCLUSIONS. 1. A slight rise of systolic blood pressure is produced in normal adults by exposure of the face to cold air. This rise persists for a varying length of time, and is often succeeded by a fall to the initial level, although the exposure be continued.

2. In 16 experiments carried out on 12 adults suffering from different infections the systolic blood pressure was increased decidedly but twice, as a result of exposing the patients to cold air.

## LEUKOCYTE AND DIFFERENTIAL COUNTS IN WARD AND OPEN AIR TREATMENT.

BY T. G. ORR, M.D.,

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FEW observations have been made comparing the leukocyte counts of patients in the usual hospital ward with counts made in the open air. Cabot[1] states that prolonged cold bathing decreases the number of white cells in the peripheral circulation and dry cold does the same. Lenkei[2] found that cold-air baths caused a rise in leukocytes in a majority of cases, amounting to as much as 9.8 per cent. Van Oordt[3] has carried out some very complete experiments along this line. He exposed naked persons to an average temperature of 7° C., making leukocyte counts immediately before and at varying lengths of time after exposure. His conclusions were that cold air causes a leukocytosis in the skin capillaries which is produced by thermotaxis, and that this leukocytosis continues as long as the naked body is exposed to the cold air. Upon rewarming the

[1] Clinical Examination of the Blood, p. 189.
[2] Pester Med. Chir. Presse, May, 1910, xlvi, No. 20.
[3] Zeit. f. Diätetische u. physikal Therapie, 1905–6, ix, 338.

skin there is a gradual decrease in the leukocytes until the end of an hour, when the change ceases, leaving, however, an absolute increase in the number of leukocytes.

Our object was not to determine if there was any transient change in the leukocyte or differential counts when patients were moved into the open air, but to learn if there was any constant difference between the counts in the ward and those out-of-doors in the regular routine treatment of bed patients.

We have made total leukocyte and differential counts upon patients at times varying from one hour to three or four days after moving the patients from the ward into the open air, or from open air into ward. The time allowed to elapse between the counts depended upon the nature of the case. In cases that were apt to have marked changes in the number of white cells, the counts were made with only a few hours intervening, and those in which there was little change clinically, counts were made at longer intervals. In the open air only the face of the patient was exposed. All but 3 of our patients were kept constantly in bed during the experiments. To avoid digestion leukocytosis nearly all of the counts were made from three to five hours after a meal. Digestion leukocytosis, however, is hardly to be considered in the febrile cases, because of their comparatively low proteid diet. In the latter cases the counts were made at the height of the disease, and crises or sudden changes in the intensity of the infections were avoided.

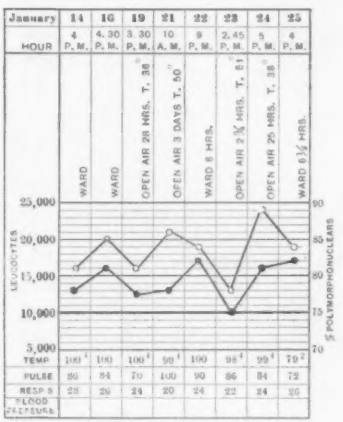


FIG. 1.—Leukocyte chart of febrile case.

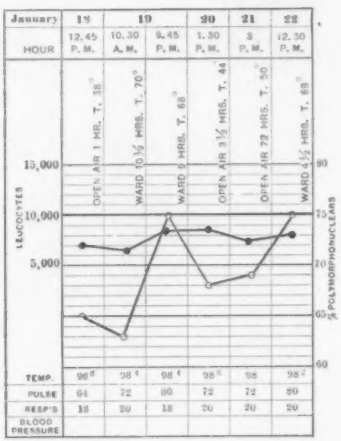


FIG. 2.—Leukocyte chart of afebrile case.

In making the differential counts, attention was given only to the percentage of polymorphonuclears, they being the cells of chief interest in a majority of acute infections.

The method of charting the counts is shown in the accompanying leukocyte chart (Figs. 1 and 2). This chart was suggested to us by the charts used by Gibson[4] and Hewitt[5] in their papers on the leukocyte and differential counts in acute surgical diseases. Ten thousand leukocytes and 75 per cent. polymorphonuclears are considered the upper limits of normal, and are placed on the same normal line in the chart.

Observations were made upon 10 afebrile and 8 febrile patients. The accompanying table shows the results obtained.

| Disease. | Ward. | | | | | Open air. | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Average temperature of ward. | Average temperature of patient. | Number of counts. | Average total leukocytes. | Average percent. of polymorphonuclears. | Average temperature of air. | Number of counts. | Average total leukocytes. | Average percentage of polymorphonuclears. | Percentage of increase or decrease of total leukocytes. | Percentage of increase or decrease of polymorphonuclears. |
| **Afebrile Patients.** | | | | | | | | | | | |
| Tenotomy (postoperative) | 68° | 98.2 | 3 | 8,500 | 49.3 | 25° | 3 | 9,166 | 48.6 | + 7.8 | —1.4 |
| Entamebic dysentery (convalescent) | 68° | 98.4 | 3 | 8,166 | 71.3 | 32° | 2 | 6,750 | 75.0 | —17.3 | +5.2 |
| Syphilis of liver | 68° | 98.5 | 3 | 9,377 | 82.2 | 36° | 3 | 9,333 | 84.3 | — 0.4 | +2.5 |
| Chronic cardiac valvular disease | 68° | 98.6 | 2 | 6,750 | 54.5 | 34° | 3 | 7,166 | 58.6 | + 6.1 | +7.5 |
| Pharyngitis (convalescent) | 68° | 98.6 | 2 | 9,000 | 63.0 | 47° | 2 | 9,250 | 61.5 | + 2.7 | —2.4 |
| Constipation | 68° | 98.6 | 3 | 7,500 | 71.0 | 41° | 3 | 7,666 | 67.3 | + 2.2 | —5.2 |
| Hernia (postoperative) | 68° | 98.2 | 2 | 8,750 | 60.0 | 40° | 2 | 9,000 | 57.5 | + 2.8 | —4.1 |
| Hernia (postoperative) | 68° | 98.4 | 1 | 7,000 | 71.0 | 30° | 1 | 6,000 | 72.0 | —14.2 | +1.4 |
| Hernia (postoperative) | 68° | 99.0 | 3 | 12,166 | 68.6 | 32° | 3 | 11,666 | 68.6 | — 4.1 | |
| Malaria (convalescent) | 68° | 98.6 | 2 | 9,000 | 50.5 | 52° | 2 | 8,000 | 47.0 | —11.1 | —6.9 |
| **Febrile Patients.** | | | | | | | | | | | |
| Lobar pneumonia | 68° | 104.1 | 3 | 11,333 | 93.6 | 37° | 3 | 11,833 | 94.6 | + 4.4 | +1.0 |
| Lobar pneumonia | 68° | 102.3 | 2 | 10,500 | 89.5 | 28° | 4 | 10,375 | 89.5 | — 1.2 | |
| Lobar pneumonia | 68° | 103.1 | 3 | 27,500 | 90.0 | 39° | 3 | 27,166 | 89.6 | — 1.2 | —0.4 |
| Lobar pneumonia | 68° | 103.5 | 2 | 16,250 | 89.5 | 24° | 3 | 14,833 | 90.6 | — 8.7 | +1.2 |
| Serofibrinous pleurisy | 68° | 100.5 | 3 | 8,333 | 77.3 | 33° | 2 | 7,500 | 74.5 | — 9.9 | —3.6 |
| Chronic pulmonary tuberculosis | 68° | 102.2 | 5 | 8,600 | 78.2 | 27° | 5 | 8,200 | 75.0 | — 4.6 | —4.1 |
| Chronic bronchitis | 68° | 100.0 | 4 | 15,377 | 83.5 | 35° | 4 | 12,777 | 83.5 | —16.8 | |
| Acute bronchitis | 68° | 101.5 | 3 | 19,166 | 84.0 | 19° | 3 | 19,833 | 87.0 | + 3.4 | +3.5 |

Of the afebrile patients, there were 5 who showed an increase and 5 a decrease in total leukocytes, 4 an increase, 1 no change, and 5 a decrease in the polymorphonuclear counts. The total leukocytes of 2 of the 8 patients with fever were increased and 6 decreased in the open air. The polymorphonuclear percentages were increased in 3 cases, they were unchanged in 2 and decreased in 3 cases.

Conclusions. 1. There is no constant change in the total leukocyte or polymorphonuclear counts in afebrile patients when

[4] Annals of Surgery, April 1906, xliv, 485.
[5] Ibid., December 1911, liv, 721.

treated in the open air with only the face exposed as compared with counts in the ward.

2. In the majority of patients with fever and leukocytosis there is a small percentage decrease in the total leukocytes when treated in the open air with only the face exposed as compared with the count when treated in the ward. Under like conditions there is no constant change in the polymorphonuclear counts.

These experiments were carried out at the House of Relief in the service of Dr. T. B. Barringer, to whom I am much indebted for advice and assistance in the preparation of this paper.

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## FATAL PNEUMOTHORAX FOLLOWING EXPLORATORY PUNCTURE.[1]

By Hughes Dayton, M.D.,

Associate Attending Physician, New York Hospital.

In a paper on Accidents and Deaths from Exploratory Puncture of the Pleura,[2] the statement was made that the importance of pneumothorax after exploratory puncture depended upon the condition of the patient at the time of its occurrence and upon the physical state of the perforated lung, which might permit contraction of the puncture or favor extreme or progressive pneumothorax. This was based entirely upon a study of cases in the literature as no instances of this accident were found in the records of the New York Hospital during the twelve and a half years under consideration. Since then 2 fatal cases of this character have forced the conclusion that the physical state of the opposite lung may be of even greater importance.

Case No. 175,676, a widow, aged fifty-eight years, was admitted to New York Hospital on February 7, 1912, complaining of pain in the chest and cough. The only significant portion of her previous history was that of chronic cough for many years. In February, 1911, she was treated in the New York Hospital for an attack which was diagnosticated as pneumonia and resembled it in history, blood findings, and course, though the sputum was never blood-tinged. Cough continued until the present illness. About December 29, 1911, she had cough, chills, and fever every night, moderate sputum, never blood-tinged, and pain in both chests increased by coughing. Since January 4 she had been confined to bed and had lost considerable weight. On February 7, examination showed emaciation. Over both lungs there were slightly woody resonance, high-pitched

[1] Read before the New York Academy of Medicine, Section on Medicine, May 21, 1912

[2] Surg., Gyn., and Obstet., 1911, xiii, 607.

voice, and occasional sibilant and subcrepitant rales. Posteriorly, over the left base, where signs of consolidation had been present a year before, were impaired resonance and diminished breathing. The sputum was scanty, thick, mucopurulent. Six specimens were negative for tubercle bacilli. The temperature usually ranged between 98° F. and 101° F. or less each day, with respirations at first 36 to 46, later 22 to 26, and pulse 92 to 104. The urine was that of chronic interstitial nephritis. The leukocytes numbered about 10,000, of which about 70 per cent. were polymorphonuclears. On February 22 the left chest posteriorly from the seventh rib to the base and extending out four inches from the median line showed dulness and many subcrepitant rales; over the upper part of this area were bronchial breathing, voice, and whisper.

Two days later I noted in the seventh and eighth spaces, about two to two and a half inches from the median line, a small area over which cavernous breathing and whisper were heard only after productive cough. After unproductive cough there were heard coarse, almost musical moist rales. Within a few minutes after coughing the signs suggestive of a cavity would disappear completely excepting occasional rales. Below the above area were dulness, diminished breath and voice sounds to the base of the lung. The patient's general condition improved and she was allowed to sit up. On the morning of March 5, she did not feel well and had some dyspnea. At 8 A.M. the temperature was 102°; respiration, 24; pulse, 100. Physical signs were unchanged. Aspiration of the right chest was ordered. Hearing of this, I reached the ward just as a needle had been inserted, at 4.45 P.M., in the sixth right intercostal space just internal to the vertebral border of the scapula. The needle was carefully inserted about one inch and nothing obtained. The patient complained, immediately after its withdrawal, of intense pain at the site of puncture and in the front of the right chest, then showed severe and increasing dyspnea and cyanosis. Signs of subcutaneous emphysema appeared over an area three or four inches in diameter around the site of puncture. Over the entire right chest were dull tympany and very distant breath sounds. The right border of cardiac dulness was displaced from the right to the left sternal margin. A diffuse apex-beat was indistinctly felt in the fifth space 13 cm. out. At 4.55 P.M., systolic blood pressure was 90, pulse 108, feeble and irregular in frequency. Magendie's solution, caffeine sodiosalicylate, and adrenalin were administered, but the patient became more cyanotic and was unconscious by 5 P.M., when blood pressure was only 60, pulse 120. The note over the right chest gradually became more dull and lost its tympanitic quality. Through a needle inserted in the third right interspace in the midclavicular line air was expressed during expiration, apparently not under good pressure. Death occurred at about 5.10.

Autopsy by Dr. R. G. Stillman showed the diaphragm extending to the fifth interspace on the right side and to the fourth on the left. The right lung seemed collapsed in part and the heart was displaced to the left. The right pleural cavity was dry and was filled over the apex of the upper lobe of the lung with dense fibrous adhesions. The puncture wound in the sixth right intercostal space, 5 cm. from the median line, occupied a position where the pleura was free from adhesions and corresponding to the apex of the lower lobe. The right upper lobe was somewhat lacerated by its removal but otherwise appeared normal. The surface of the lower lobe was smooth, glistening, and grayish-pink. No evidence of a puncture of the lung was found. A few encapsulated fibrous nodules were scattered through this entire lung. Two or three of these were calcareous. The left pleural cavity was entirely obliterated by firm adhesions. The left lung on section presented a dark-red surface from which on pressure a moderate amount of red, frothy fluid exuded. Along the posterior border of the lower lobe was an area of indurated tissue, about 4 by 9 cm., in which could be seen a multilocular cavity occupying almost all of this portion of the lung. The lining of this cavity was smooth. Opening into it were two or more dilated bronchioles. The bronchial mucous membrane was deeply injected and covered with mucopus. The walls of the bronchi appeared to contain an excessive amount of cartilage which in many places exhibited calcareous infiltration. Besides these signs of adhesive pleurisy at the right apex and right pneumothorax, with chronic pleurisy and chronic fibroid phthisis with cavity formation in the left lung, other lesions included those of chronic interstitial nephritis, chronic interstitial splenitis, perihepatitis, fibrous goitre, and a calcified uterine fibroma.

Of the possible causes of pneumothorax, entrance of air through the needle can be positively excluded, as the needle was attached, before introduction, to a Connell vacuum bottle with active suction. That air could not have entered subsequently through the puncture wound in the chest-wall was shown by the presence of a drop of blood over the wound until it was closed with collodion. That it was not the result of laceration of the adherent right apex was shown by the absence of signs of antemortem hemorrhage in any of the lacerations produced during removal of the lung at autopsy. Although no puncture hole could be found in the lung, the occurrence of a small perforation by the needle seems proved by exclusion. Operation upon the chest would have been ineffective because the asphyxia was due to the collapse of the only serviceable lung.

The chief object in reporting this case is to emphasize the statement made in my previous paper[3] that the greatest danger exists in puncturing cases in which chronic inflammatory processes are

[3] Loc cit.

present. That assertion was made with reference to the danger of causing hemorrhage or pleural reflexes when puncturing the diseased lung. As regards the production of pneumothorax, some claim that it is most likely to occur when pleural adhesions are present or consolidation of the lung prevents closure of the puncture. Others think it occurs most often when the pleura is normal and the lung diseased, especially when there is softening in the lung near the pleural surface but not involving it. In the case which I have reported and one to which I shall refer briefly, the punctured lung tissue was absolutely or practically normal.

When the patient's general condition is not too poor, when the perforated lung is in such physical condition as to permit closure of the puncture and so prevent extreme and progressive pneumothorax; and when the opposite lung is in good condition, unilateral pneumothorax may pass almost unobserved. In a patient (2S 58, 486) who died in the New York Hospital in 1897 of acute pancreatitis after his right chest had been repeatedly explored, the autopsy showed pneumothorax of the right pleural cavity. The right lung was collapsed and inflation under water showed two small punctures, but the lungs were otherwise normal. In this case there were no subjective symptoms of pneumothorax.

A second case of fatal pneumothorax following exploratory puncture was a longshoreman, aged thirty-nine years, who was admitted to the Medical Division (No. 181442) on February 29, 1912, apparently suffering from lobar pneumonia involving the right lower lobe. Fever continued and signs of consolidation of the right lower lobe and the apex of the upper lobe persisted, especially near the spine of the scapula, where they suggested an interlobar empyema. Two punctures near the apex of the right lower lobe yielded no fluid. Signs of a suppurative process in the left shoulder developed and the patient was transferred to the Surgical Division. An abscess was drained by an incision through the deltoid muscle. The pus contained streptococci. A septic temperature continued; the *x*-rays showed infiltration of much of the right lung, and signs of consolidation of the apex of the right upper lobe became more marked. A large subcutaneous abscess appeared behind and below the left shoulder and this was incised. At about 2.30 P.M on April 12, a needle was inserted in the upper portion of the left chest posteriorly in search of other collections of pus. A few minutes after this puncture the patient complained of a choking sensation and became dyspneic with profuse sweating. Physical signs of pneumothorax developed in the left chest and death from asphyxia occurred at 12.10 A.M. on April 13.

Autopsy by Dr. Schultz showed universal, thick, pleural adhesions over the right lung which was filled with innumerable tubercles. The apex of the left lung contained many tubercles and the overlying pleura was adherent. The rest of the lung was collapsed. The

site of the puncture was not found, but was probably in or near the adherent pleura. There was osteomyelitis of the scapula and head of the humerus involving the shoulder joint. As in the first case, it was the almost complete disability of the unwounded lung which led to the fatal termination from pneumothorax.

The point which I would emphasize above all is that the most serious and sudden results of the occurrences of pneumothorax due to exploratory puncture follow injury, not of the diseased, but of the efficient lung, when, as in two of the cases reported, the diseased lung is so incapacitated by consolidation and adhesions as to be incapable of adjusting itself to the unusual task. In the presence of a chronic inflammatory pulmonary process we are thus confronted with a choice of evils. Puncture of the area of chronic consolidation may result in hemorrhage or serious accident from pleural reflexes; puncture of the opposite normal lung may cause fatal pneumothorax. It is true that puncture of a normal lung rarely causes pneumothorax, but when it does do so, under such circumstances as existed in the cases reported, it is equivalent to signing a death-warrant. With these facts before us the conclusion seems inevitable that in the presence of probable chronic inflammatory disease of the lung, exploratory puncture should be restricted to cases in which there are good reasons for suspecting the existence of purulent exudate which would require surgical treatment.

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## TUBERCULIN THERAPY IN SURGICAL TUBERCULOSIS.

By Thomas Wood Hastings, M.D.,

Professor of Clinical Pathology in the Cornell University Medical College, New York.

### PART I. ARTICLES AND MONOGRAPHS.

Koch's Era. The use of specific therapy in tuberculosis began with the era established through the discovery of Koch's tuberculin. Koch[1] recommended the injection of old tuberculin after careful experimental work upon healthy and tuberculous guinea-pigs.

Among the first to experiment upon the same line were two investigators in this country, Trudeau[2] and de Schweinitz,[3] both of whom obtained results corroborating Koch's experimental work, and it is safe to say that since their time no more important and convincing experiments have been done along the same line. In reviewing the literature dealing with experimental active immunization for tuberculosis, one is impressed with the fact that experimental evidence in favor of injection of tuberculin is far from

convincing; on the other hand, when one studies the literature of tuberculin therapy relating to the treatment of patients afflicted with chronic and resisting forms of tuberculosis, one is impressed with the fact that tuberculin is an extremely useful adjunct to the better known methods of therapy. We have had little experience with pulmonary tuberculosis, and for a consideration of this subject the numerous papers by Koch,[1] Petruschky,[4] Goetsch,[5] Mueller,[6] Turban,[7] Weicker,[8] Spengler,[9] Baudach,[10] Trudeau,[11] Denys,[12] and Sahli[13] should be consulted. More recent papers by younger observers, Hammer,[14] Hamman and Wolman,[15] Hyslop-Thompson,[16] Lowenstein,[17] Turton,[18] Bonney,[19] Pottenger,[20] Bandelier,[21] Raw,[22] Dluski,[23] record results which are very much in accord and in favor of the use of tuberculin, even in ambulant cases of pulmonary tuberculosis. Attention is particularly directed to the non-pulmonary forms of tuberculosis—tubercle-bacillus infections, which involve other parts of the body, and with rare exceptions, not involving the lungs, so far as one may determine by physical examination—cases coming under the term of surgical tuberculosis, using the term surgical in its broadest sense to denote invasions of the skin, eye, ear, abdominal organs, and bone. The literature relating to tuberculin therapy in surgical tuberculosis is relatively scanty, for the surgeons as a rule, have been infrequent contributors to the records on immunization and experimental therapy. Much of the convincing literature is hidden away in the excellent monographs on tuberculin by Petruschky,[4] Kohler,[24] Denys,[12] Birnbaum,[25] Beitzke,[26] Daels,[27] E. Klebs,[28] M. Koch,[29] Orth and Rabinowitsch,[30] Luedke,[31] Sahli,[13] Weicker,[8] Bandelier and Roepke,[21] Kohler and Lenzmann;[32] and excellent reports of cases are to be found in articles beginning in 1896 with that of Liebmann[33] and including Nathan Raw's[22] article in 1910. Numerous articles which appeared during these years (1896–1910), will be referred to under the divisions relating to parts affected.

In the *Lancet* for September 17, 1910, p. 885, there is recorded a lengthy discussion by Wright, Latham, Hewlett, Walters, Warner, and Lawson. These observers, with Wright, agree that the proper use of tuberculin, in both surgical and pulmonary cases, is a great step in advance in therapy. Latham[34] concludes that tuberculin is a most potent remedy, which is most efficacious in non-pulmonary forms. Permanent cures for periods over two years in most desperate cases were recorded by him, and he does not hesitate to give tuberculin during pyrexia as high as 105° F. He quotes Ritter, of the Edmundsthal Heilstaette, in Hamburg, as having used tuberculin in minute doses many years ago.

Emery[35] says that its best use is limited to surgical cases, with numerous disappointments and numerous successes—and in conjunction with other methods, tuberculin has its place.

Walters[36] explains that tuberculin is likely to be of service in

two classes of cases: (1) Those in which the slightest exertion causes excessive auto-inoculation (auto-toxosis), and (2) those in which exercise has little immunizing effect.

Nathan Raw[37] has treated with Koch's tuberculin (humanus) 110 surgical cases, including adenitis, peritonitis, arthritis, lupus, meningitis, pyonephrosis, cystitis, and prostatitis. In localized forms, most of them of bovine origin, Koch's tuberculin (T. R.) had excellent effect; except in those with encysted pus. In these cases he claims the danger of causing dissemination with resultant blood serum infection. If any tendency to suppuration appears the glands must be opened, but no extensive dissection of glands is indicated in principle and sometimes it leads to generalized tuberculosis. In peritonitis tuberculin has splendid effect, and with operation and drainage many cases remained completely cured. In genito-urinary cases from ten to seventeen injections have an excellent healing effect, when everything else has failed. Raw does not separate "open" and "closed" cases.

These more recent experiences coincide with and are often more enthusiastic than the numerous reports from the larger experiences of Petruschky,[4] Sahli,[13] Goetsch,[5] Denys,[12] Calmette,[38] Beraneck,[39] Rosenbach,[40] and Trudeau;[11] and there is a definite consensus of opinion, among those who have studiously used tuberculin for many years, to the effect that tuberculin therapy is efficacious, and should find a permanent place among methods of treatment.

## PART II. THEORY OF IMMUNIZATION.

It is interesting to refer to Koch's original theory of immunization. Koch[1] found by injecting healthy guinea-pigs with pure cultures of tubercle bacilli that after a period of from ten to fourteen days there developed at the site of the injection a hard nodule, and that after a certain longer period this nodule softened and ulcerated progressively until the animal's death.

Experimental Immunity in Guinea-pigs. Entirely different results were obtained when a tuberculous guinea-pig was so inoculated. The most striking results were obtained in animals which survived infection from four to six weeks. In such animals the inoculation wound scabbed over quickly, but no nodule formed, and on the second and third day a peculiar change appeared at the site of injection, which consisted in a hardness and a dark discoloration spreading about the site for from 1 millimeter to 1 centimeter.

On the fourth day the skin had become necrotic and sloughed off and there remained a flat ulceration, which generally healed quickly and permanently, without infiltration. The guinea-pig infected with tuberculosis had, through the first injection, obtained

such a degree of immunity that the second injection did not take hold.

Use of Killed Cultures. Koch found further that the killed pure cultures of tubercule bacilli, triturated in water, when injected in large quantities into healthy guinea-pigs produced only suppuration; and that, on the other hand, in tuberculous guinea-pigs small quantities of the suspended culture caused death within a short while. By methodically repeated use of higher dilutions it was possible to preserve the life of the animal and to bring about a marked improvement.

Absorbable and Non-absorbable Products. It was shown that there was no resorption at the site of the injection and that the suspension remained in the tissue and aroused suppuration. The healing substance must therefore have been thrown out from the bodies of the tubercle bacilli, while the substance which produced suppuration remained behind or was very slowly dissolved. Efforts to extract the healing substance from the bacilli led Koch to the discovery of tuberculin.

Today we know that the substance from the bacilli, acting as antigen, arouses the body tissues to the production of healing substances. Koch thought the healing reaction due to a specific effect upon the tuberculous tissue (bactericidal immunity) resulting in necrosis and healing, and was to be obtained by rapidly increasing the dose. Today we know that from the tuberculin injections, in addition to a local effect upon the focus of infection, there is also immunization against bacterial poison dependent upon bacteriolytic processes which free endotoxins or endoproteins and upon phagocytosis; and that immunity is best obtained by inoculation of small doses slowly increased over a long period of time.

Types of Immunity after Tuberculin Injections. According to the knowledge relating to immunization which has accumulated since Koch's time, one must consider two types of artificially acquired active immunity: (1) Antitoxic; (2) antibacterial, *a*, bactericidal; *b*, bacteriolytic (resulting in ant-endotoxic, or ant-endoprotein immunity); *c*, phagocytic, (1) bacteriotropic, (2) opsonic.

Immune Bodies in Immune Blood. One may conclude with Spengler,[41] that immune bodies of immune blood in tuberculosis may be agglutinin, precipitin, opsonin, chiefly lysin, and antitoxin (ant-endotoxin), but one cannot agree with him in regard to the mechanism of their formation.

The theory that the action of tuberculin is partly antitoxic (Bandilier and Roepke[21]), is untenable, since the production of soluble toxins by the healthy bacillus has never been proved, and the isolation of endotoxin has not been accomplished; and further, the work of Koch,[1] Maragliano,[42] and Wassermann and Brueck[43] particularly, has proved that immune bodies can be

recovered in the tuberculous focus and also in the blood of man after the tuberculin injections.

ISOPATHIC IMMUNITY. Isopathic immunity has been suggested by but few experimenters, among them von Behring,[44] and more recently Webb,[45] who suggested and tried the injection of living bacilli, beginning with a single bacillus, which was carefully obtained by a particularly delicate technique.

IMMUNIZATION WITH KILLED BACILLI. Most methods of immunization have been based upon injection of dead bacilli, and it should be recalled that Koch obtained his best results by the injection of bacilli killed by heat; and that Bordet and Gengou,[46] and Dembinski[47] obtained markedly different results between the use of living and dead bacilli, in favor of dead bacilli.

Trudeau,[48] in 1907, discussed antitoxic, antibacterial, and isopathic immunity, and inclined toward the belief in antitoxic and antibacterial immunity in tuberculosis; and in 1909, accepted the antitoxic theory of immunization as particularly appropriate for tuberculosis; and one will find today that most investigators who are familiar with tuberculin immunization believe in the antitoxic —not in the sense of diptheria antitoxin—and the antibacterial theories, when considering the substances which should be used for injection.* This may not seem clear, but the day has come when one must consider the possibility of separating products which are particularly poisonous to the human organism and without a marked curative effect, from other substances which are less poisonous and which have a greater curative power. The latter substance or substances should be relatively greater than the former substance or substances in any preparation, such as tuberculin, which is injected for therapy. In 1901 Bordet and Gengou[49] described the complement absorption method for the detection of specific amboceptors. In 1903[46] they reported the experimental production of such specific amboceptors in guinea-pigs injected with living avian cultures and with heated or killed human cultures. Dembinski[47] (1904) concluded that production of amboceptor against the tubercle bacillus depended upon the type of bacillus used (human, avian, bovine), and in 1906, Dembinski's idea was disproved by Gengou, who found that avian bacilli killed by heating at 65° C. for one-half hour or at 100° C. for five minutes produced amboceptor against the various mammalian tubercle bacilli, and that the variation in the amboceptor production depended upon the animal, in that it was less marked in rabbits than in guinea-pigs. Gengou, likewise, found that injection of one type of the acid-fast bacilli, saprophytic or pathogenic, would give

* The reaction for good or bad is supposed today to be due to the action of a tuberculoprotein upon hypersensitive tissues. For the relation of hypersensitiveness (anaphylaxis) to tuberculin in immunity to tuberculosis, refer to Wolff-Eisner,[51] and Trudeau, Baldwin, and Krause.[52]

amboceptors against nearly all the other mammalian tubercle bacilli, and he recalled the fact that Klemperer had obtained the same results in his earlier experiments upon guinea-pigs. The application of results of the experiments of Bordet, Gengou, and Dembinski to the study of tubercle bacillus infections, with or without tuberculin injections, was first made by Wassermann and Brueck,[43] who concluded that the specific reaction in infectious disease is due to the fact that the focus reacts to the metabolic (*stoffwechsel*) products of its specific antigen, in such small quantities that no marked effect is noted on an organism free from this infection. This was first shown for tuberculin, and diagnostic and therapeutic procedures are based on this specificity. The local (in the diseased tissue) reaction is far more impressive than the general reaction, with rise of temperature.

EXPERIMENTAL STUDIES ON THE WORKING OF TUBERCLE BACILLI PREPARATIONS IN TUBERCULOUS ORGANISMS. Anatomico-pathological changes in the diseased tissue with specific reaction have been much studied. In *resume:* Under injection of tubercle-bacillus preparations, in tuberculous foci there are signs of a flooding with body fluids and an infiltration with the ameboid cells of the blood; consequently a softening and dissolution of the tissue.

Just as old as the studies on the tissue are the investigations for an explanation of the reaction in the diseased tissues. There are many theories. According to Rappoport[50] the tuberculous organism in the sense of von Behring is toxine-hypersensitive.

ADDITIONS-THEORIE. Babes[50] believes that in tuberculous foci tuberculin already exists, and that the tuberculin injected results in summation. Ehrlich's[50] theory, in explanation of the local reaction assumes that the focus, as a bulb, is surrounded by many cell layers. The innermost layer is saturated with tubercle bacillus products (tuberculin), the middle layers are injured through the products, and the outer layer is completely uninfluenced and sound. Injected tuberculin acts neither on the inner saturated, nor on the outer healthy, but on the middle already damaged cell layer. Why the tuberculous focus attracts to itself minimal quantities of a certain tubercle bacillus preparation in the blood stream, and how the entrance of tuberculin into the focus is followed by softening and destruction of tissue, are questions which Wassermann and Brueck attempted to answer.

IMMUNE BODY IN PATIENTS AND ANIMALS NOT INJECTED WITH TUBERCULIN. They reasoned, since lupus cases react to from $\frac{1}{10}$ up to 1 milligram and the average blood mass is 5 kilos (=5000 c.c.), that if 1 milligram be injected the dilution in the blood is 1 to 5,000,000. Such an amount injected into a lupus focus produces no local reaction. So the entire tuberculin mass by some substance in the focus is drawn out from the circulating blood and then concentrated on the focus. So there must be a

haptophore group (an antituberculin) for the injected tuberculin, in the focus. And one must prove in the tuberculous focus: (1) Presence of the tuberculin-like substance in solution, and (2) reaction products and antibodies for these substances (antituberculin). They employed the Bordet-Gengou complement-fixation method. Rabbit-sheep amboceptor and guinea-pig complement were used.

Antituberculin in Organ Extracts. Organs or tuberculous portions were rubbed in a mortar with 0.8 per cent. salt solution and 0.5 per cent. carbolic (1 gram of organ to 5 c.c.), shaken twenty-four hours at room temperature and centrifugated. Certain quantities of the clear extract with decreasing amounts of tuberculin (A. T. and B. E.) and $\frac{1}{10}$ c.c. of pure guinea-pig complement were kept at 37° C. for one hour. Then hemolytic unit was added and kept for from one to two hours at 37° C. and, later, over night on ice. Inhibition in certain tubes proved the presence of antituberculin in tuberculous organ extracts of human lung and glands, and organs from guinea-pigs and cattle.

Antituberculin in Blood Serum. They found also antituberculin occasionally in the serum of guinea-pigs and cattle; but in 13 human cases, not handled specifically, in all stages of lung tuberculosis there was no trace of antituberculin in blood serum. Antituberculin in the organs requires the presence of tuberculin. To prove this, they replaced the tuberculin with a good agglutinating serum (from Hoechst) and found tuberculin in tuberculous organ extract, human and mammalian, but not in serum of man, guinea-pig, or cattle. That the two, tuberculin and antituberculin coexist, may in this instance be so.

Immune Bodies in Patients or Animals, or Animals Treated with Tubercle Bacillus Preparations. Antituberculin was found (1) in serum of men injected with tuberculin, after three doses of 1, 5, and 10 milligrams of A. T. No reaction occurred to A. T. and B. E. Before injections, B. E. and A. T. were not active specifically in all cases. No antituberculin was found (2) in normal cases injected with tuberculin. Thus we are concerned with not simple toxic substances, but body substances of the bacillus type. One must not conclude that these tuberculin amboceptors are identical with amboceptors against the tubercle bacillus.

Febrile Reaction. The febrile reaction depends upon two factors: The first, since it occurs in health following too large a dose, partly non-specific; the second, as a direct result of specific working of tuberculin on the tuberculous tissue, partly specific from soluble digested products being absorbed.

In injected cases, tuberculin and antituberculin combine, and thus the focus is not invaded by tuberculin and there is no marked solution of tissue and no temperature reaction, and finally, there

is no antituberculin in the tuberculous organs and, therefore, no local reaction and no temperature.

Wassermann and Brueck conclude that the explanation of the working of tubercle bacillus preparations in the tuberculous organism may be based on the following: In a large number of tuberculous individuals not treated with specific therapy, there were present in the tuberculous tissues antibodies against the tubercle bacillus preparations. The serum was free from such substances. When one injects such an individual with specific tuberculin preparations, it is clear that the power of the preparation depends upon its avidity for the antibody. Since the last has its location in the tuberculous tissue, in like manner the tubercle bacillus preparation goes to the tuberculous organs. The local reactions, softening, and dissolution of tissue, occur after union of tubercle bacillus preparation and antibody, for complement is attracted, and whenever amboceptor and complement become concentrated, and thus workable (synergic), the pre-existing protein materials are dissolved and digested.

Through union of the tubercle bacillus preparations and antibody, the protein-digesting substance in the blood (namely, complement) is concentrated on the tuberculous tissue, not alone in the form of free digesting substance, so far as it comes from leukocytes through destruction of the last and their solution in the fluids, but also in the form of digestive strength or power which exists in the leukocytes, as shown by the small cell infiltration.

The blunting against tuberculin and the efficacy of its working depend also upon the rapidity and amount of invasion of blood stream by antibody. The best condition for a cure is that there should be antituberculin in focal tissue and little or merely a trace in the blood. The worst is that in which there is little antituberculin in tissue and more in the blood. In healthy man, non-tuberculous, after 1, 5, or 10 milligrams without reaction there was found no antituberculin in serum. This is not so for opsonin.

The specific action of tuberculous tissue occurs because the tuberculins, through their antibodies, are drawn to the tuberculous tissue, and by this process the tissue-softening power of the organism is concentrated in one place. The blunting occurs because the fore-treatment with the tubercle bacillus preparations produces antibodies in the blood.

Marmorek[51] attempted to prove the presence of a "tuberculous" (not tuberculin) substance (toxin?) in the blood serum of tuberculous patients, by complement deviation tests with patients' serum and antituberculous sera from injected animals. This tuberculous substance is a related toxin, and the injection of tuberculin acts as an irritant upon the focus of infection, which calls forth the increased flowing out of toxin and thus the production of antitoxin sufficient for healing. May this not be the same as liberation of endotoxin or endoprotein through bacteriolysis?

ANAPHYLAXIS. Emery[35] thinks the tuberculin reaction similar to serum anaphylaxis of guinea-pigs. Tuberculin is, in itself, non-toxic for a normal animal, just as is serum. The tubercle bacilli possibly produce it in small amounts, resulting in anaphylaxis and the wasting and fever may be akin to the phenomenon of Arthus—the reaction of a hypersensitive animal to repeated small doses of a non-toxic substance. If this is the fact, we may regard tuberculin as the true toxin of the disease.

Emery[35] states, however, that the actual toxin and mode of action of the tubercle bacillus tuberculin are unknown. Tuberculin is not a true toxin, for immunized animals are still susceptible to the tubercle bacillus, and one can prepare a serum antitoxic for tuberculin without curative or prophylactic virtues; and tuberculosis may be afebrile. The temperature of phthisis is mainly due to secondary organisms.

Sahli[52] has used Koch's old and new tuberculin, Denys' tuberculin, and chiefly Beraneck's tuberculin and has reported the same. The curing process depends upon desensitizing the organism against the chemical tuberculosis poison. It depends upon making the tissues poison fast (mithridatismus) and is best explained by Maragliano[53] and Wassermann and Brueck,[53] as an increase of the natural ability of the body.

PHAGOCYTIC AND OPSONIC THEORIES. Metchnikoff[54] years ago proved that living germs are taken up by leukocytes and destroyed, and that phagocytosis usually occurred in mild infections and little or none occurred in fatal infections. He considered this of greatest importance in immunity and thought it should cover the whole field. Baumgarten[54] and Sanarelli[54] noted that recovery occurred when little phagocytosis was found. They described bacteriolysis in collodion bags placed in the peritoneal cavity and, later, others recognized the importance of some substance acting on the bacteria and enhancing phagocytosis—this substance coming from the leukocytes.

Kanthac and Hardy,[54] on frogs, found that eosin cells gave off substances which acted upon the bacteria and hyaline cells. When they injected such bacteria in man, a similar process occurred in which the injurious substances came from polynuclears, which are also phagocytes.

Metchnikoff[54] later described macrocytase from macrophages, which digest cells; and microcytase, from polynuclears, which acts against bacteria.

THERMOSTABILE OPSONIN FOUND. Wright was antedated by Denys and Leclef[55] (in 1895), Mennes and Markl,[56] and Neufeld and Rimpau,[57] who found thermostabile oposonin for streptococcus and pneumococcus. Wright elaborated and described independently the opsonin, and strongly advocated the use of vaccines.

Wright[74] states that no disease is more truly a local one: Im-

munity to tubercle bacillus is local rather than general. The main curative agency is due to phagocytosis; but this does not necessarily depend upon the same mechanism noted *in vitro* in the study of opsonins.

The result of tuberculin injection is very complex, and it is at least possible that the curative effect is due to reaction in or near the lesion—very small doses cause a definite local reaction best seen in tubercles of the iris, which are surrounded by a hyperemic zone after 1 milligram of T. R. or B. E.

So far as is known the polynuclear leukocytes act only on the bacilli in the circulating blood. Normal tuberculo-opsonin is completely thermostabile, and the rise in index with or without injections is due to the same. Thermostabile opsonin is never abundant, and not constant. Wright,[54] [58] denies the demonstration of any lytic or cidal elements and little is known of any other antibody. No antitoxin is known. Wassermann and others have shown such antibodies in patients after tuberculosis, but their action is unknown.

Mueller[59] says that there is no doubt of the variation in opsonin and in the phagocytic index but this is no explanation of the immunizing reaction. Opsonin does not vary with bacteriolytic power, but seems independent of complementary and bacteriolytic substances, and of agglutinin. This was shown by Wright and Bullock[60] and by Torrey.[61] Serum opsonin is multiple, and varies much with individual types of bacteria; with any type, extremely virulent organisms are not phagocytible, as shown by Hektoen and Rosenow.[62] The opsonin here referred to by Mueller is bacteriotropin, or immunopsonin.

Normal Opsonin in Contrast to Immunopsonin. He believes that normal opsonin and bacteriolysin are practically identical, in contrast to which immunopsonin (or bacteriotropin) has nothing to do with bacteriolysin. Mueller accepts Wright's classification of bacteria, based upon reaction to the various immune bodies: (1) Bacteria, little affected by opsonins and bactericidal substance, such as cholera and typhus. (2) Bacteria, highly sensitive to opsonin and bacteriolytic substances; coli and dysentery. (3) Bacteria, highly sensitive for opsonin; not so for bacteriolytic substances; Staphylococcus aureus, Micrococcus melitensis, pneumococcus, Bacillus pestis. (4) Bacteria, not sensitive to opsonin or to bacteriolytic substances; diphtheria and xerosis. He does not venture to place the tubercle bacillus in any one of these classes.

Allergie and Immunity. Von Pirquet's[63] "allergie" refers to the hypersensitiveness of all the body tissues, and is primarily concerned with the diagnostic reactions. Immunity remains the term for any instance of allergie in which a useful hypersensitiveness and increased resistance are attained.

After becoming conversant with the literature, one decides that

the theories for artificial immunization against tuberculosis are individualistic in part, depending upon the line of research which has engaged the attention of the individual investigator; and that the immunizing mechanism follows the several theories combined. This is well presented by Mueller in his lecture on "Infection and Immunity."

MUELLER'S THEORY. Mueller[59] states that if the infectious microörganisms invade the body tissues in any way and find the proper physical (osmotic pressure) and chemical (reaction, nourishment) conditions for growth, they begin to multiply. A part of these newly produced germs come in contact with the bactericidal substances already on hand in the locus invaded, and, by these substances, are killed and decomposed. The body substances of the bacilli thus freed, as well as the secretions from them, lure the leukocytes from the tissues and the blood which either through active secretion or through disintegration, provide new bacteriohostile substances for the tissue fluids, and so cause the renewed killing of the infectious germs. A part of the killed microörganisms are taken up by phagocytes and transported; but living germs, also, having been acted upon by opsonin, can be taken up by the white blood cells and either go to their death or multiply, and after they have destroyed the host cells, go free again.

The toxins produced by the living germs, as well as those going into solution from the bacterial bodies, call forth in the neighborhood of the infected locus more or less extensive anatomico-pathological changes which, according to the kind and intensity of the irritant, show as inflammation, suppuration, necrosis, and tissue proliferation.

With the fluid circulation, the toxic substances pass to the distant organs and produce the changes noted as intoxication signs (ecto- or entotoxosis). Meanwhile, the combat goes forth from the locus of infection. Each succeeding generation of microorganisms is more virulent.

On the other hand, the defensive reaction can persist; the mass of protective stuff or, speaking directly, phagocytosis, is increased. The phenomena of extracellular bacteriolysis takes on a greater significance, although single germs invade the blood stream, to be destroyed or to lodge in the capillaries of some organ.

TWO FACTORS INFLUENCING OUTCOME. Mueller states that the final favorable or unfavorable outcome depends upon two different factors: Whether the organism is able to check the bacteriobiosis (bacterial growth) and to destroy pathogenic germs; and, whether it can endure the toxic effect of the metabolic products—the toxin —and the disintegration products—the proteins and endotoxins —of the bacteria. The lethal result may be grounded upon two factors: The relative insufficiency of the detoxicating (apotoxinizing) preparedness after the germs are killed and dissolved; or,

the general failure of the bacteriolytic and phagocytic defences. In the first, the bacteriological examinations of fluids and blood will be negative; in the second, the tissues and blood will be flooded with microörganisms. Between the two forms, toxemia and bacteriemia, all possible transition stages are found.

Mueller agrees with Wassermann and Brueck. The specific tuberculin reaction is due to avidity of the tuberculous focus for union with the injected tuberculin; and the reaction is a concentrated one.

Wolff-Eisner[64] adds that the antituberculous substance possesses the character of a bacteriolytic amboceptor, which, on account of the tubercle-bacillus splitting due to the injected tuberculin, sets free the endotoxin-like (endotoxinoid) poison, and thereby brings about an enhanced toxic reaction.

Wassermann's and Brueck's idea of the tissue lysis due to the digestive action of the bound complement is more comprehensive.

The absence of antituberculin in the blood of the tuberculous individuals who have not been injected with tuberculin and the local antibody production calls for an increase of sessile receptors with no throwing off of these receptors into the blood stream, according to Mueller. (This is not necessarily so; unless one has examined the blood of patients under all conditions of activity and inactivity, which has not been done, for the processes may alternate.)

It is quite possible, in view of Wassermann's and Brueck's and Citron's[65] observations, that the invasion by a secondary microörganism in a pulmonary focus is more likely than in a non-pulmonary focus, for complement action after fixation at site, causing dissolution of tissue must lower resistance to bacteria other than tubercle bacilli.

## PART III. KINDS OF TUBERCULIN

TUBERCULINS. The different preparations known as tuberculin are substances, in the media, produced by the tubercle bacilli during growth, substances extracted from the tubercle bacilli, or the bodies of the tubercle bacilli themselves before or after extraction. The injection of tuberculin results in active immunization, and the tuberculins are in no sense serums, as is the popular misconception, for the term serum is continually used even by the medical profession in speaking of the use of tuberculin. The accompanying list by no means exhausts the tuberculins which have been described but contains those most written about and used.*

* See Bandelier and Roepke, loc. cit., ref. 21, pp. 140 to 188.

LIST OF TUBERCULINS.

| Variety. | Originator. | Date of introduction. |
|---|---|---|
| A. T. or O. T., old tuberculin, original | Koch | 1890–1891 |
| (T. A. K. or T. A., Denys) | | 1891 |
| Tuberkulocidin | Klebs | 1896 |
| Antiphthisin | Klebs | 1896 |
| Tuberkuloprotein | Klebs | 1896 |
| T. O., Obere Tuberkulin | Koch | 1897 |
| T. R., rest tuberculin (Neutuberculin T. R.) | Koch | 1897 |
| Tuberkuloplasmin | Buchner and Hahn | 1897 |
| Oxytuberkulin | Hirschfelder | 1898 |
| Tuberkulol | Landmann | 1898–1900 |
| B. E., Bacillary Emulsion (Neutuberkulin-Bazillenemulsion) | Koch | 1901 |
| T. Bk., Tuberkulin | Beraneck | 1903–1905 |
| Bovine tuberculin (Perlsuchttuberkulin) | Spengler (see Note) | 1904–05–07 |
| Nastin | Deycke and Reshad-Bey | 1905 |
| B. F., tuberculin Denys (broth filtrate) | Denys | 1905 |
| Tuberkulin, CL (Tuberculine Calmette) | Calmette | 1906 |
| Tuberkulase | von Behring | 1906 |
| Tulase | von Behring | 1906 |
| Tulaselaktin | von Behring | 1906 |
| Watery extract | von Ruck | 1897–1906 |
| Tuberkulo-cidin-selenin | Klebs | 1907 |
| Tuberkulonastin | Deycke and Reshad-Bey | 1907 |
| Tuberculo-albumin | Piorkowski | 1908 |
| Tuberkulo-sozin | Klebs | 1908 |
| Tuberkulin, IK | Spengler | 1908–1909 |
| "Sensitized Bacillus Emulsion" | Citrone | 1909 |
| Tuberkulin, "weakly toxic" | Rosenbach | 1910 |
| Endotin, "poison-free" tuberculin | Gordon | 1910 |
| Tuberculin, "albumose-free" Koch's tuberculin | Jochmann and Möller | 1910 |
| "Sensitized Bacillus Emulsion," "non-poisonous" | *Wolff-Eisner | 1910 |

NOTE.—Tuberculins of Carl Spengler, 1904–05–07: (*a*) *A. T. O.*, original alt Tuberkulin, vakuum Tuberkulin; (*b*) *P. T. O.*, Perlsuchttuberkulin original, Perlsucht vakuum Tuberkulin; (*c*) *T. B. E.*, Tuberkelbazillenemulsion, Perlsucht Bazillenemulsion; (*d*) *T. B. V.*, Tuberkelbazillen Vakzin Perlsucht Bazillenvakzin.

A. T. AND O. T., OLD TUBERCULIN USED NOW CHIEFLY FOR DIAGNOSIS. The old tuberculin of Koch[67] (A. T. or O. T.) is no longer recommended for therapy, but still remains the best preparation for calling forth the various tuberculin reactions for diagnosis. Hunter[68] and Trudeau[69] were among those who early modified the original or produced new tuberculins. Trudeau in 1892 described a broth filtrate which was practically identical with Denys' (1905). Koch[70] was the first to improve upon his original tuberculin (O. T.), which was simply the glycerin broth medium, upon which the bacilli had grown, concentrated to one-tenth its volume, and preserved by the addition of carbolic acid to ½ per cent. The improvement consisted of the separation of the watery extract, or fluid, in which the bacilli were ground up with a pestle, from the resulting residue which consisted of powdered tubercle bacilli.

T. O. AND T. R. The fluid portion was called Tuberculin "Obere" (T. O.) and the powdered residue Tuberculin "Residuum" or

"Rest" (T. R.). Tuberculin T. R. (tuberculin residue) is prepared from the living, dry, virulent tubercle bacilli, triturated in an agate mortar. The powdered bacilli are suspended in distilled water and centrifugalized, and the supernatant fluid which has the properties of old tuberculin is Obere tuberculin, T. O. The residue is dried, again powdered, emulsified, centrifugalized, and the uniform mass obtained is Tuberculinum residuum (T. R.), which corresponds somewhat to an endotoxin. It is diluted with 20 per cent. to 50 per cent. glycerin, and the addition of carbolic acid is not advised.

Dosage by Weight. There is confusion in regard to dosage, for 1 gram of dried tubercle bacilli is used in preparation of each 100 c.c., so that each cubic centimeter of the remedy contains the material from 10 milligrams of bacilli. But the amount of dry residue is only one-fifth of this amount, so that 1 c.c. of T. R. contains 2 milligrams of solid substance. The dosage adopted concerns the dry residue only, viz., 1 c.c. equals 2 milligrams. This tuberculin should be heated to 0° C. before use.

T. R. or Rest Tuberculin (New Tuberculin). Tuberculinum residuum, T. R., was also called "New Tuberculin," and should not be confused with the more recently described "Bacillus Emulsion," which is also termed "New Tuberculin."

B. E., Bacillus Emulsion, or New Tuberculin. The last, described by Koch[71] in 1901, is a suspension of the bacilli in normal salt solution, thoroughly ground and shaken, so that the fragments of the bacilli are suspended in the fluid, and so prepared that 1 c.c. contains 5 milligrams of the dried powdered bacilli in equal parts of glycerin and water. This is probably the nearest approach attainable to the unmasking of the endotoxins through mechanical means. Several attempts have been made to modify the general toxic action, and to enhance the desired immunizing action through treatment of the bacilli with various chemicals, and by utilizing the combination of the less toxic with the more toxic substances after the isolation of both.

T. Bk., Tuberculin Beraneck. Such a tuberculin is that of Beraneck,[39] which is the mixture of phosphoric acid extraction of the tubercle bacilli and the concentrated broth in which the bacilli have been grown. This has been described as a mixture of basotoxic and acidotoxic (b. t. + a. t.). Conflicting reports (Sahli[13] and Dluski[72]) are concerned with the use of Beraneck's tuberculin, and Sahli, after years of experience, recommends it as the best preparation. It is supposed to contain ectotoxin and entotoxin, and to be much less toxic than old tuberculin.

Toxicity of Tuberculins. If one may judge from reactions after injections, Beraneck's preparation is much less toxic than many others. Also, from reactions after injections, one must consider that Denys'[73] broth filtrate is most toxic; for reactions

with temperature are not infrequently obtained after the most minute doses of this dilute tuberculin. Denys' broth filtrate (B. F., B. F. H.) is prepared from cultures grown in beef peptone broth with 5 per cent. glycerin. After growth for several weeks, the cold broth is filtered through paper. Phenol to 0.25 per cent. or a little thymol is added to kill any bacilli and as a preservative. The preparation contains the inactive substances, peptone, glycerin, and meat extractives not utilized by the bacteria; the "disassimilation" products of the bacteria, probably ferments, diastases, and albuminoid substances perhaps among them the tuberculo-nuclein of von Behring and, finally, products from the disintegration of dead bacilli. The concentrated filtrate should be kept cold in the dark. The diluted filtrate will not retain its properties more than three or four weeks.

Effect upon Temperature. The susceptibility of the infected organism to broth filtrate led many to conclude that this preparation is of much value in reducing temperature in febrile cases, and that such can be done will be shown later by reference to Fig. 2, after Denys. That the same effect may be obtained through the Bacillus Emulsion (Koch) will be shown by Figs. 1 and 3. The most recent attempts to prepare more acceptable tuberculins have been along the lines adopted by Beraneck; that is, decreasing the general toxicity and increasing the immunizing power by various means.

Tuberculin Rosenbach. Rosenbach[40] has prepared a tuberculin by growing tubercle bacilli several weeks old in symbiosis with a fungus (Tricophton holosericum album), grinding up the residue and filtering and mixing this filtrate with the filtered culture medium. He believes that the changes in the complicated proteins, produced through enzyme action, greatly reduce the general toxicity, which is borne out through his experience and by his statement that the initial dose may be as high as 1 to 2 decigrams, and that 1 centigram is a small dose.

Comparison of Tuberculins as to Advantage. The preparations of Landmann,[74] von Behring,[75] Hirschfelder,[76] Calmette,[38] Klebs,[77] Piorkowski,[78] Deycke and Reshad-Bey,[79] and von Ruck,[80] have no advantages over and apparently are not so useful, judging from results, as the preparations of Koch, Denys, Berancek, and possibly Rosenbach. Sigismund[81] has recently compared the potencies of the tuberculins of Landmann, Beraneck, and Koch, and has found Landmann's preparations "D" five times, and "C" ten times more potent than that of the standard (Koch's) tuberculin; and Beraneck's three and three-tenths times weaker than Koch's. This potency refers to the "toxicity" and not necessarily to the immunizing power.

Doubtful Value of Bovine Tuberculin for Human Therapy. Spengler's[82] idea that tuberculin prepared from bovine strains would

prove most efficient, an idea borne out experimentally by the work of Bordet and Gengou, has not found acceptance with those who have had the most experience with tuberculin. Spengler's[83] more recent articles on tuberculin IK, suggest that his later procedure may have value; but from his results, a value not so great as that of the older preparations which have been tried for years.

TUBERCULIN CL. Calmette's[38] tuberculin CL is not well known. Strong concentration, less toxicity, production of no fever, with increasing opsonic index, leading to healing, mark this form. Tuberculin CL contains the secretion products from the bacilli in the culture medium, as well as the protoplasmic substances of the bacilli bodies extractable in vacuo with glycerin, precipitable in cold by absolute alcohol, non-dializable with ether, and soluble in physiological salt solution. Its potency is one thousand times that of Koch's old tuberculin.

TUBERCULOUS IMMUNE-BLOOD IMMUNE-BODY THERAPY OF SPENGLER. The immune-body therapy (tuberculin IK) of Spengler[83] is not a true passive immunization, but a passive-active one, because the lytic substances dissolve the infectious germs so that the poison through resorption leads to active immunization. This IK is chemically pure, free from albumin and blood pigment, and is the product from immune blood of artificially immunized healthy men and animals. It has a direct antitoxic and lytic bactericidal effect.

Hewlett[85] and Citron[86] suggest that endotoxins after Besredka's method might be more potent; that is, mixing the bacteria with immune serum, and thus sensitizing them before injection, particularly for preparation of prophylactic vaccine.

It is interesting to note that Garbat and Meyer[87] have produced or prepared a typhoid serum after Besredka's method.

SUMMARY OF BEST PREPARATIONS TODAY. When we recognize the probability that antitoxic and antibacterial immunization should be considered the most satisfactory, the simpler methods of combining injections of Denys' broth filtrate and bacillus emulsion (Trudeau and Brown), and old tuberculin and the new tuberculin (Petruschky, 1904) recommend themselves as the best to date; particularly, for pulmonary invasion, where the toxic symptoms are more marked than in the surgical conditions.*

## PART IV (SECTION 1). ADMINISTRATION.

Administration may be by (1) hypodermic injections, (2) digestive tract (*per orem*), (3) suppositories. For years the hypodermic

* For recent articles relating to new preparations of nature of tuberculin refer to: Landmann,[84] Hollos,[84] Gordon,[88] Endotin (a poison-free tuberculin). Jochmann und Möllers[89] (Albumose-free tuberculin). Gabrilowitsch,[90] Wolff-Eisner[91] (Sensitized tubercle bacillus emulsion), Meyer.[92]

injections of tuberculin were alone considered. Administration by the digestive tract has been practised and written of by Calmette[93] (1908), Moeller[94] (1908), Hyslop Thomson[95] (1909), and Latham,[34] particularly.

Method Per Orem, English School, Latham, Walters. Latham still recommends it by mouth, on an empty stomach, early in the morning. The method is most strongly praised by the English school. Walters[96] states that by mouth it may be successfully administered, but often causes pain and nausea, and the effect of the dose is uncertain. Warner finds that administration by mouth is successful, but not suitable for every case. Inman believes that tuberculin so given can be absorbed by the stomach. Lawson supports Latham's oral administration, and by him the needle is rarely employed.

Suppositories. Administration by suppositories was attempted by Lissauer.[97]

Choice of Cases for Tuberculin Treatment. In relation to administration, the general pathology of surgical tuberculosis must be considered a moment, for the success in any one instance depends in part upon the selection of cases, or more upon the selection of the proper period during the infection in any one case through which to continue the injections. It may be right, in the one instance, to institute tuberculin therapy before operation and before submitting to hygienic-dietetic treatment; to operate and give tuberculin; to treat surgically alone; to treat hygienically and administer tuberculin; or to combine all these methods. To avoid criticism in regard to tuberculin methods, we have treated, with few exceptions, those cases which have not responded encouragingly to, or have been classed as improper for, surgical treatment, after thorough trial in competent hands.

It is paramount and must be kept continually in mind that the patient, while receiving tuberculin injections, should be under the best conditions of hygiene, diet, and rest obtainable for each case, and that developments such as pus formation and injury to bone should be at once handled surgically; for under such developments we may be dealing with a secondary infection, and the general organism and the focus of infection has to be in a cleansed condition to respond properly and permanently to the tuberculin stimulus.

Petruschky[4] made much of this necessity for toning up each case in order to obtain a proper response, and of properly classifying cases according to their pathogenesis. In 1897, Petruschky[4] described three typical stages, similar to the development of lues without the primary lesion, in the pathogenesis of tuberculosis considered as an early invading and long developing disease.

First Stage. The primary stage is that of lymph node infection as in the scrofulous type of child, existing in the cervical glands,

in adenoid vegetations, bronchial glands, mesenteric glands; with or without symptoms of poisoning. Those conditions supposed in part to be predisposing, were thought by Petruschky to indicate tuberculous intoxication.

SECOND STAGE. The second stage—that of metastasis development, results in meningeal, pleural, peritoneal, miliary forms, and marks the beginning of processes in skin, bones, joints, and lungs.

THIRD STAGE: "OPEN" TUBERCULOSIS. To the third stage belong the ulcerative pulmonary (phthisical) tuberculosis, bone caries, and ulcerative lupus. In this stage the processes are complicated by secondary infection with other microörganisms and constitute the pathogenetic condition of "open" tuberculosis.

"CLOSED" TYPE OF PRIMARY AND SECONDARY STAGE. The primary and secondary stages are the forms of "closed" tuberculosis, in which the tubercle bacilli are not cast off externally, and therefore, imply that the cases are not directly infectious. In studying and classifying our cases of any one anatomical type —glands, eye, kidney, bone—we have strictly adhered to consideration of them as "open" and "closed" in the sense used by Petruschky.

One realizes at once that the "closed" cases, considered as immunizable organisms, present a more favorable prognosis than the "open," unless, perhaps, the latter are to be treated with autogenous (autochthonous) vaccines, or specific antisera for the secondary invasion.

SECONDARY INFECTIONS. There is no doubt, from pathological changes in tissue and from clinical symptoms, that, as a rule, the secondary infection influences unfavorably the course of the disease. According to Petruschky, the claim of Koch that tuberculin (O. T.) is a certain cure against incipient tuberculosis was not far from the truth; suitable for the tuberculin therapy, also, are the "open" cases, in which there is not marked destruction of the organs involved and the general health is relatively good.

NOT GIVEN IN CACHEXIA. Since tuberculin is not a direct-acting substance (as is diphtheria antitoxin) one must expect the organism to possess sufficient strength to react to the toxic material, so that extremely asthenic cases are not suitable for injections. In such individuals first build up strength by good hygiene and food and then use tuberculin. One may add today: Reduce the initial dose in asthenic cases and *do not hesitate to use tuberculin.*

IN FEBRILE CASES: IS TEMPERATURE DUE TO SECONDARY INFECTION? Petruschky[4] also advised against tuberculin in febrile cases, but Denys,[12] Latham,[34] Walters,[36] Inman,[98] and Nathan Raw[37] do not agree with the majority, who hold to Petruschky's belief. With us, as with others, the effect upon temperature has seemed to be dependent upon dosage. Upon those who refuse to inject tuberculin in febrile cases rests the burden of proving that

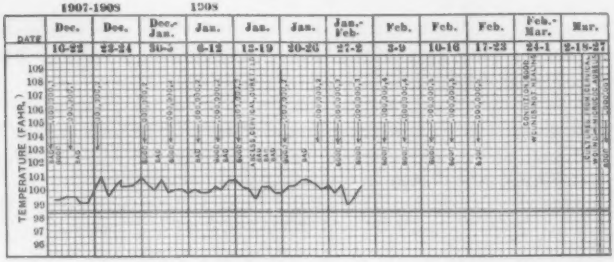



FIG. 1, Section 1.

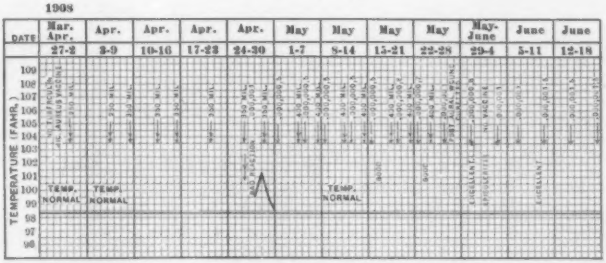



FIG. 1, Section 2.

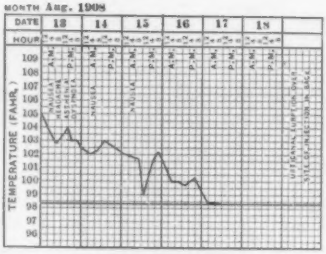



FIG. 1, Section 3.

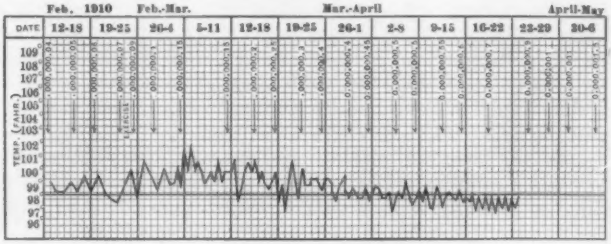



FIG. 1, Section 4.

FIG. 1.—Chart from a case in which temperature persisted although well tuberculinised, until an autogenous vaccine was administered.

the temperature is not often due to secondary microörganisms which may cause the fever, and at the same time would not respond to tuberculin.

Real and Apparent Tuberculin Temperature. Fig. 1 shows the chart from a case which shows what may be taken for proof of such a condition, for when well tuberculinized the temperature persisted, but came down after an autogenous vaccine was administered; and later, when wounds were free from staphylococci, the temperature, which had arisen after tuberculinization had worn out, fell rapidly after a few tuberculin injections.

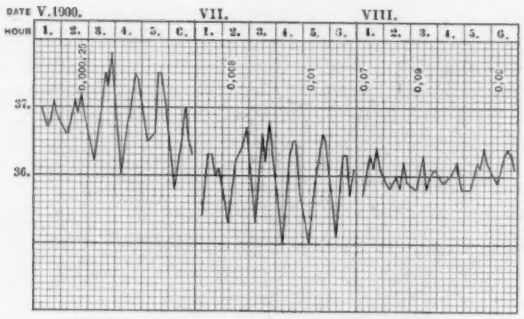



Fig. 2.—Shows lowering of slight temperature and finally reduction in oscillations under tuberculin. (From Denys.)

In Fig. 3 is shown the fall in temperature coincident with improvement, in a case of tuberculous peritonitis. The rise in temperature to 102° F. eight days after the last injection followed the Fourth of July, and certainly was not due to the tuberculin injection, but may have been an autotoxic reaction following too violent exercise and excitement, although it was attributed to a digestive disturbance. The child has remained well since that time.

Febrile Usage. Walters,[96] in dealing with pulmonary tuberculosis, does not fear tuberculin in highly febrile cases and considers it chiefly or mainly a question of dosage and agrees with Latham in that minute doses will bring down temperature. Lawson[99] thinks that in pyrexia of the pulmonary cases it does not reduce fever and no longer gives it during pyrexia; he makes no reference to surgical cases.

The Use of "Series" of Inoculations. Petruschky,[4] in 1904, spoke from an experience with many thousand inoculations over a period of thirteen years. Of great importance is Petruschky's statement that most cases, particularly of "open" type, will not go to complete healing with one "kur;" the best term for which, with us, is "series." He recommends often eight to ten series.

After eight to ten weekly injections, a pause of like duration is made and then the "series" is repeated. It is advisable to change the tuberculin preparation; one series being given with old tuberculin, and the others with the new preparations, in order to fortify the body against all the toxic substances of the tubercle bacilli, according to Petruschky.

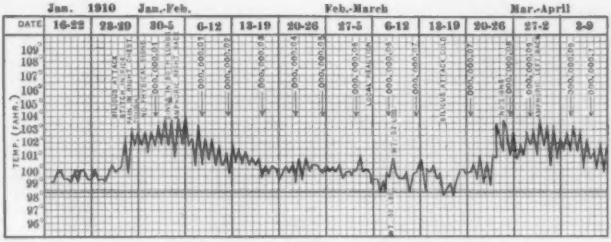



FIG. 3, Section 1.

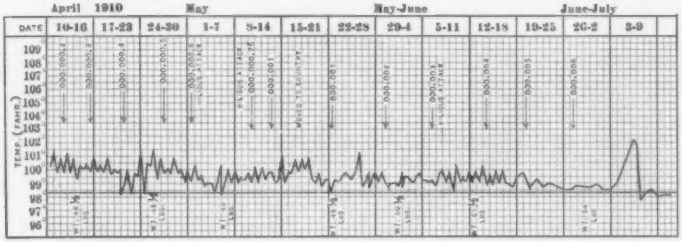



FIG. 3, Section 2.

FIG. 3.—Chart from a case of tuberculous peritonitis treated with tuberculin. The fall of temperature was coincident with improvement.

## PART IV (SECTION 2). DILUTION AND DOSAGE AND INTERVAL OF DOSAGE.

DOSAGE OF O. T. AND T. R. Petruschky[4] recommended for a not abnormally sensitive patient, seventeen injections from $\frac{1}{10}$ milligram to 100 milligrams of old tuberculin (O. T.); 0.1, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 15, 25, 35, 45, 60, 80, 100, making seventeen doses. For tuberculinum residuum (T. R.) he advises fifteen injections from 0.1 milligram to 100 milligrams; 0.1, 0.3, 1, 2, 3, 5, 5, 7, 10, 15, 25, 35, 45, 60, 80, 100, making fifteen. From experience most investigators consider such doses too high. Between any two injections he allowed at least two free days. After a febrile reaction or pain and tenderness at injection site, the last dose was to be repeated instead of increased, and after a strong

reaction the amount of the last dose was to be reduced and a pause of four to eight days allowed.

Dosage B. F. and B. E. Denys; Trudeau. The system of dilution followed when no other is specified is that, in principle, originally used by Petruschky and modified for smaller doses by Denys. Trudeau was among the first to follow such a method, and it might as well be called Trudeau's as Denys'.

Reference to the following table after Denys[12] will indicate the dilution and dosage.

DOSAGE: SERIES OF DILUTIONS.

| | | | |
|---|---|---|---|
| 1. | T-III | = | Bouillon, pure |
| 2. | T-II | = | dilution at tenth |
| 3. | T-I | = | dilution at hundredth |
| 4. | T-0 | = | dilution at thousandth |
| 5. | T-0/10 | = | dilution at ten thousandth |
| 6. | T-0/100 | = | dilution at hundred thousandth |
| 7. | T-0/1000 | = | dilution at millionth |
| 8. | T-0/10000 | = | dilution at ten millionth |

| | | | | Pure tuberculin. |
|---|---|---|---|---|
| 0.1 c.c. | T-0/10000 | (dilution at ten millionth) | = | 0.00000001 |
| 0.1 c.c. | T-0/1000 | (dilution at millionth) | = | 0.0000001 |
| 0.1 c.c. | T-0/100 | (dilution at hundred thousandth) | = | 0.000001 |
| 0.1 c.c. | T-0/10 | (dilution at ten thousandth) | = | 0.00001 |
| 0.1 c.c. | T-0 | (dilution at thousandth) | = | 0.0001 |
| 0.1 c.c. | T-I | (dilution at hundredth) | = | 0.001 |
| 0.1 c.c. | T-II | (dilution at tenth) | = | 0.01 |
| 0.1 c.c. | T-III | (pure) | = | 0.1 |

(After Denys.)

This gives eight strengths for dilution, each reduced to one-tenth strength, in terms of cubic centimeters for B. F. and in terms of grams and milligrams for B. E.

The dosage according to Sahli[13] is based upon the method of dilution of Beraneck, as shown below in the table.

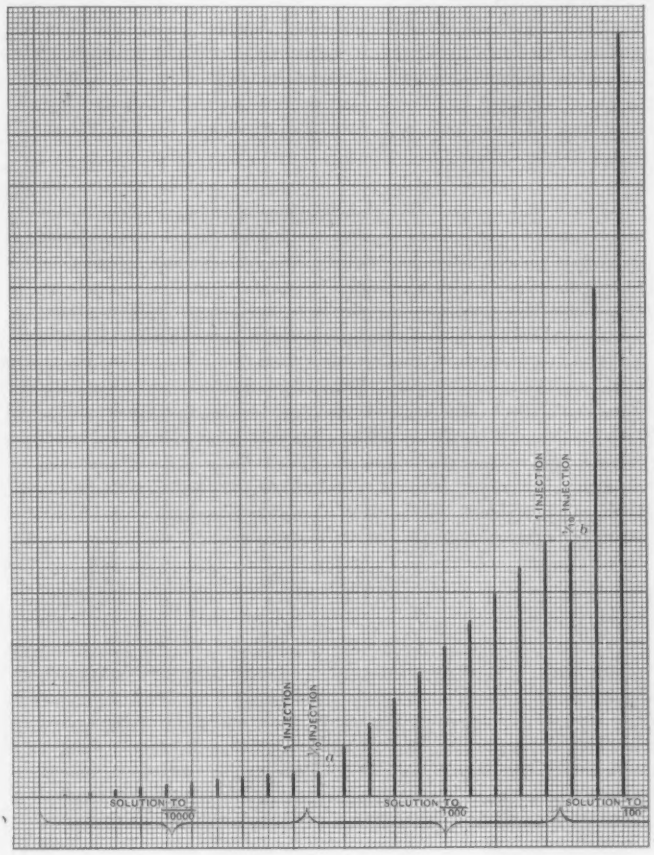
| Solution of tuberculin, Beraneck: | | | (Pure tuberculin, Beraneck) | | |
|---|---|---|---|---|---|
| H | = | TBk | | | |
| G | = | TBk/2 | A/2 | = | TBk/256 |
| F | = | TBk/4 | A/4 | = | TBk/512 |
| E | = | TBk/8 | A/8 | = | TBk/1024 |
| D | = | TBk/16 | A/16 | = | TBk/2048 |
| C | = | TBk/32 | A/32 | = | TBk/4096 |
| B | = | TBk/64 | A/64 | = | TBk/8192 |
| A | = | TBk/128 | A/128 | = | TBk/16384 usw. |

(After Sahli.)

Prepared in thirteen dilutions, each following solution is one-half the strength of the foregoing. Such dilutions permit of a gradual, regular increase in dosage.

When compared to Denys' method, the one usually employed, the difference is striking as shown in Fig. 4.

SAHLI: DENYS. By Denys' method the rate of increment changes with each new dilution on the tenth, twentieth, and

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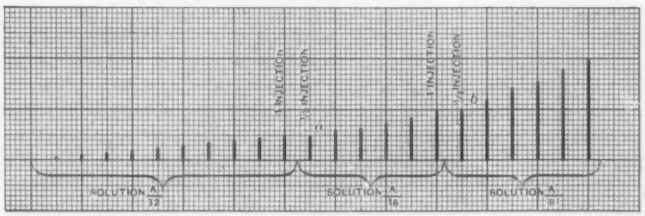


2.

FIG. 4.—(1) Denys' dilution scale. (2) Beraneck's dilution scale. (After Sahli.)

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Dosage B. F. and B. E. Denys; Trudeau. The system of dilution followed when no other is specified is that, in principle, originally used by Petruschky and modified for smaller doses by Denys. Trudeau was among the first to follow such a method, and it might as well be called Trudeau's as Denys'.

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| 7. | T-0/1000 | = | dilution at millionth |
| 8. | T-0/10000 | = | dilution at ten millionth |

| | | | | Pure tuberculin. |
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| 0.1 c.c. | T-0/10000 | (dilution at ten millionth) | = | 0.00000001 |
| 0.1 c.c. | T-0/1000 | (dilution at millionth) | = | 0.0000001 |
| 0.1 c.c. | T-0/100 | (dilution at hundred thousandth) | = | 0.000001 |
| 0.1 c.c. | T-0/10 | (dilution at ten thousandth) | = | 0.00001 |
| 0.1 c.c. | T-0 | (dilution at thousandth) | = | 0.0001 |
| 0.1 c.c. | T-I | (dilution at hundredth) | = | 0.001 |
| 0.1 c.c. | T-II | (dilution at tenth) | = | 0.01 |
| 0.1 c.c. | T-III | (pure) | = | 0.1 |

(After Denys.)

This gives eight strengths for dilution, each reduced to one-tenth strength, in terms of cubic centimeters for B. F. and in terms of grams and milligrams for B. E.

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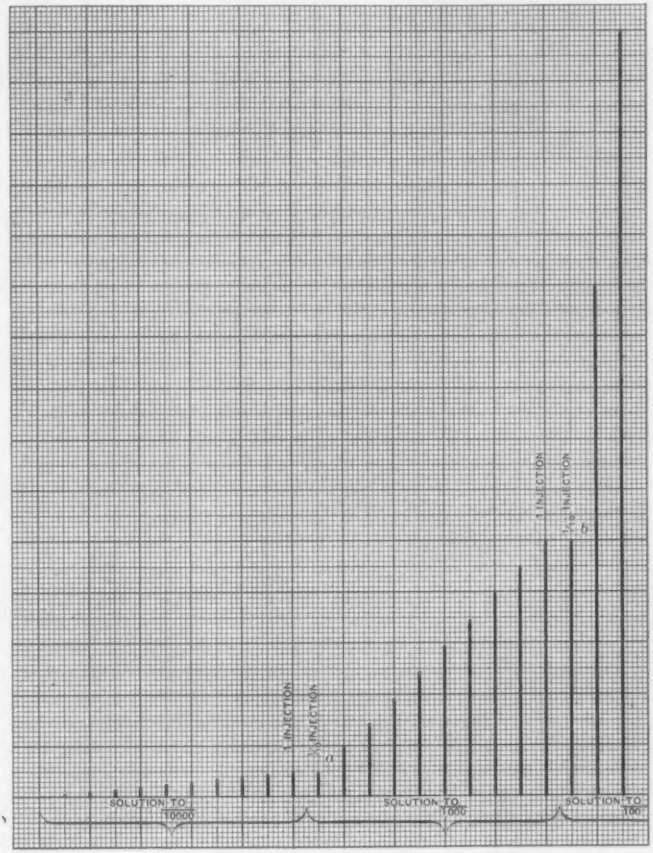
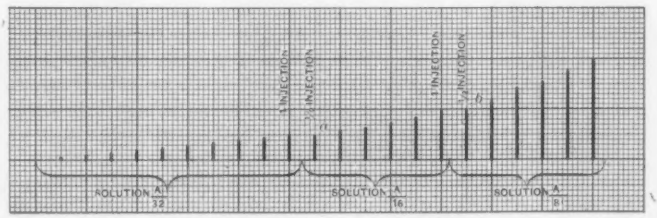



1.




2.

FIG. 4.—(1) Denys' dilution scale. (2) Beraneck's dilution scale. (After Sahli.)

thirtieth doses, which in theory is not so desirable as the regularly graduated increment. Unless some further evidence is brought against it, however, there is no reason for not employing Denys' method.

Brown[100] has proposed an increase by logarithmic scale, based upon dilution in tenths, after Denys' method of dilution, but each injection is varied to the logarithmic scale to meet any desired number of doses per cubic centimeter, as illustrated in the accompanying table.

SUGGESTIONS FOR DOSES OF TUBERCULIN

1. These should be from 0.0000001 to 1.2 for B. F. (Never higher than 0.005 or 5 milligrams for B. E.)
2. If there are reactions, begin with a dose of 0.00000001.
3. Continue B. F. and B. E. by giving B. E. $\frac{1}{200}$ of B. F. dose. (Brown.)
4. Increase according to logarithmic scale:

| Doses: 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| 3.2 | 2.2 | 1.8 | 1.6 | 1.5 | 1.4 | 1.3 | 1.3 | 1.3 | 1.2 | 1.2 |
| 10.0 | 4.7 | 3.2 | 2.5 | 2.2 | 2.0 | 1.8 | 1.7 | 1.6 | 1.5 | 1.5 |
| | 10.0 | 5.6 | 4.0 | 3.2 | 2.7 | 2.4 | 2.2 | 2.0 | 1.8 | 1.8 |
| | | 10.0 | 6.3 | 4.7 | 3.7 | 3.2 | 2.8 | 2.5 | 2.3 | 2.2 |
| | | | 10.0 | 6.8 | 5.2 | 4.2 | 3.6 | 3.2 | 2.9 | 2.6 |
| | | | | 10.0 | 7.2 | 5.6 | 4.7 | 4.0 | 3.5 | 3.2 |
| | | | | | 10.0 | 7.5 | 6.0 | 5.0 | 4.3 | 3.8 |
| | | | | | | 10.0 | 7.7 | 6.3 | 5.3 | 4.7 |
| | | | | | | | 10.0 | 8.0 | 6.6 | 5.6 |
| | | | | | | | | 10.0 | 8.0 | 6.8 |
| | | | | | | | | | 10.0 | 8.3 |
| | | | | | | | | | | 10.0 |

Whatever the method followed for dilution the initial dose is approximately $\frac{1}{10000}$ milligram of B. E. and T. R., and B. F., for the usual case, with as little as $\frac{1}{1000000}$ milligram of B. E. and B. F. for the unusual case which reacts generally to the $\frac{1}{10000}$ milligram. A simpler manner of expression is in terms of $\frac{1}{10}$ c.c. for a certain dilution, for example: For the initial dose, $\frac{1}{10}$ c.c. of a dilution of 0.000001 gram (dilution of 1 to $\frac{1}{1000}$, or $\frac{1}{10000000}$ grams), or 5 ciphers (5/1).

Thus the second dose would be 0.2 c.c. of 0.000001, and each succeeding dose would be increased by 0.1 c.c. When for any dilution a dose of 1 c.c. is reached the dilution of 0.00001, or 4 ciphers 1 (4/1), ten times stronger than the preceding, is begun, the first dose of which is equivalent to 1 c.c. of the preceding dilution.

INCREMENT OF DOSAGE, B. F., B. E. Since the increment with a higher dilution is much greater than with the preceding dilution

for each successive dose, one is likely to see general reactions following an injection of a next higher dilution so that it is wise to note carefully the effects of the first three or four injections and to repeat, rather than increase, the dose for the first few injections of the higher dilution.

In some cases the new dilutions should be fivefold and not tenfold the former dilution, and the initial dose 0.2 c.c., equivalent to 1 c.c. of the former dilution.

Frequency of Dosage, B. F., B. E. The frequency of injection should not be oftener than twice a week for the smaller doses. Yet this varies with the tuberculin, for Denys recommends the daily injection for a few days at a time, and Sahli also suggests daily injections for Beraneck's tuberculin. For T. R. and B. E. the frequency should be twice a week, for dilutions up to 0.00001 (4/1), and once a week for from 0.00001 (4/1) to 0.0001 (3/1), and once in ten days or two weeks for from 0.0001 (3/1) to 0.001 (2/1).

Emery[35] recognizes three methods of injection: (1) The intensive method: T. R., $\frac{1}{1000}$ milligram two or three times a week, increasing to 2 milligrams. The patient is certainly immunized to tuberculin. (2) The opsonic method: T. R., from $\frac{1}{1000000}$ to $\frac{1}{1000}$ milligram; the first dose controlled by and the optimum dose and interval determined by the phagocytic index. (3) The use of small doses without opsonic or other control: T. R., $\frac{1}{1000}$ milligram once in ten days or once a week.

The total number of injections for a series varies according to different authors with the tuberculin used, but strikes an average between twenty-four and thirty-six in all.

Calmette's Tuberculin (CL). Calmette's[38] tuberculin (CL) is given as follows: Increasing doses from $\frac{1}{1000}$ milligram to 1 milligram at twelve-day intervals. On the average a cure follows after twenty-four injections. (288 days = 41 weeks = 10 months.)

Contraindications for Dosage During Treatment. A general reaction with temperature within from six to twenty-four hours, rarely twenty-four to forty-eight, should be followed by omission of the next succeeding injection and by reduction of the dosage to one-quarter or one-half of the preceding injection. Local reaction at the injection site with marked swelling, redness of skin, induration beneath skin and tenderness (the classic rubor, dolor, tumor, calor). Finally, with swelling and tenderness of adjacent lymph nodes, repetition should be avoided and the succeeding injection should not be increased, and the interval should be lengthened sufficiently to allow two or three days of comfort after subsidence of the marked local disturbance. Focal reaction (herd reaktion) at the site of infection indicated by discomfort or actual pain, increased redness and local temperature, tenderness, and limitation of motion, when the focus is so located

that it is visible or interferes with free motion of joints, tendons or muscles, must also be avoided, and should be followed by a repetition or maybe even lessening of the last dose, as after a local reaction.

Tuberculin cachexia with loss in weight after high doses, with the tuberculous process apparently in abeyance, is not uncommon, and is a contraindication for continuing injections. When such a condition obtains, the organism should be allowed to rest for a period of three or four months or until the signs and symptoms recur.

Period of Increased Resistance. The duration of the increased resistance after a single series was first given by Petruschky as three months for certain cases, and this is readily corroborated by any one over a period of three to four years. The duration varies with the individual, for many patients seem to retain their increased resistance and remain cured for years after a single series, judging from clinical symptoms and subcutaneous tuberculin tests.

Varies with Tuberculin. The duration of increased resistance seems also to vary with the tuberculin used; for Denys found it persisted for five, twelve, and nineteen months in 3 cases. This increase over Petruschky's period of three months is, in all probability, due to the longer period of inoculation given by Denys.

Petruschky[4] in 1904, reported 2 cures (aged eight and eleven years), of cervical adenitis treated in this manner: The one with five series (etappen) over a period of four years, the other with two series over a period of a year. One would hardly recommend today such rapidly increasing doses, or such large doses ultimately; but attention should be called to Petruschky's lesson in patience and persistence, and the necessity for repeated series of slowly increasing doses over a period of from two to four years—each series of from six to seven months' duration.

Length of Time for Cure. The actual length of time for one series varies considerably with the patient and the type of tuberculin used; but for all it is a question of months and not weeks. For a clinical condition approximating a cure a single series may suffice, and more frequently two and three series are necessary, so that the length of time for a cure may run into years. Wright[58] has recently published a table showing variations from six to thirty-nine months for cures.

Our records show variations from seven to forty months. Trudeau,[101] in 1909, stated that the results to be obtained are: (1) To raise tolerance to tuberculin to the highest for each case. (2) To avoid general and focal reactions; evidence of intolerance. (3) To follow no arbitrary rule or method, but to increase according to the individual tolerance. This result is best obtained by small doses, gradually increased over a long period of time. The initial dose and the rate of increase should be selected to suit each case.

(To be continued.)

# REVIEWS

DUODENAL ULCER. By B. G. A. MOYNIHAN, M.D. (London), F.R.C.S., Senior Assistant Surgeon at Leeds Infirmary, England. Second edition; pp. 486; 78 illustrations. Philadelphia and London: W. B. Saunders Co., 1912.

THE author has conferred much on the surgical world in bringing out his work on *Duodenal Ulcer*. This the second edition is not only considerably enlarged, consisting of 486 pages as against 376 in the old edition, but it also contains a discussion of 115 additional cases operated upon for duodenal ulcer which were not reported in the first edition.

The work considers duodenal ulcer in all its aspects, from the clinical and operative standpoint, as well as from that of the postmortem table.

The writer impresses upon his reader the fact that most "functional" indigestion or "dyspepsia" is nothing but an organic lesion and that "hyperchlorhydria" *is* duodenal ulcer, a stand that many medical men fail to take.

Much importance is placed by Moynihan on the anamnesis, and he believes that if carefully and intelligently taken it aids greatly in the diagnosis. He also explains his "hunger pain" statement.

The pathology of duodenal ulcer is discussed in detail and the various types taken up and described admirably. Gurling's ulcer, uremic ulcer, ulcer associated with melena neonatorum, jejunal ulcer, carcinomatous, tuberculous, acute, and chronic ulcers all receive their due share of consideration.

The chapter on differential diagnosis and treatment is masterly, and much emphasis is placed on the possibility of there being multiple lesions in any given case, such as duodenal ulcer associated with gallstones, pancreatitis, appendicitis, etc., a very important fact to note at operation.

The surgical technique, the operations, and the factors governing their choice are clearly and concisely stated. Preoperative and postoperative treatment of all cases is described in detail. Especial attention is given to the need of haste, care, and gentleness in the presence of perforation. The various points throughout the work that the author deems important are illustrated by cuts or case histories both of which are complete and satisfying, all unnecessary details, as a rule, being omitted.

Possibly there are too many illustrations of more or less similar specimens, thus giving unnecessary bulk to the book. A few minor typographical errors and the needless repetition word for word of at least one history in two places in the text are the only other adverse criticisms we have to offer.

The work is excellent, well written, clear, and exceedingly instructive, comprising as it does, virtually all that is at present known of duodenal ulcer, its pathology, diagnosis, and treatment.

E. L. E.

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SURGERY AND SOCIETY: A TRIBUTE TO LISTERISM. By C. W. SALEEBY, M.D., F.R.S.E., Fellow of the Obstetrical Society of Edinburgh; formerly Resident Physician Royal Infirmary and Resident Surgeon Maternity Hospital of Edinburgh. Pp. 395. New York: Moffat, Yard & Co., 1912.

"THE motives and purposes of this volume are in part personal, in part, public. The personal motives are gratitude for great benefit lately received from surgery and desire to make some reparation for too hard words spoken of the surgical profession some years ago under stress of intense and honest conviction. The public motives are, to state the case for surgery and, therefore, for science, in modern society; once more to challenge the anti-vivisectionists; to demand the first of what I call the rights of mothers, from my standpoint as a eugenist; to state the women's share in this most beneficent of human achievements, and to discuss the place and needs of surgery in the new experiments for national control of disease, toward which modern politics is tending."

The paragraph above cited, which is prefixed as a note to this volume, speaks for itself. The book is serious like the author, who with many other zealous men feels his duties in regenerating mankind weigh heavily upon him, and no doubt, sympathizes with the psalmist, who, after explaining that the earth and the inhabitants thereof were dissolved, added "I bear up the pillars of it."

There is no doubt whatever that few intelligent persons will not profit by reading this book. It is interesting in its historical aspects no less than in its statement of present conditions and its prophecy of the future. The descriptions of "Surgery as it Was," of the changes introduced by anesthesia, and of the newer and more rigorous obligations imposed by the discoveries of Pasteur and by all that is connoted in the word Listerism, give graphic pictures of many things which the public ought to know for their own self-protection and that of their families and children, but

of which many even of the most highly educated persons are lamentably ignorant.

Though the author takes the only sensible ground about the vivisection question, his feelings toward the anti-vivisectionists cannot be described as other than intemperate. He recognizes that they are striving for the same ends as is Listerism, but he loses his temper with them because they are dull heads, slow fools, ignorant jackasses (he does not use these words). One might as justly lose his temper with a cow because she could not catch mice, or with an idiot because he could not understand a problem in the differential calculus. "Answer not a fool according to his folly."

The question of microbes, of sepsis, and antisepsis is brought home to every dweller in cities by demonstrating that every large city has only one day's supply of fresh food between it and starvation, and that the *preservation* of food by some means is fast becoming a necessity. "When the fundamental problems of civilization come under serious review by persons who know that they must be solved, and who are thinking not of the next election, but of the next generation, the whole question of what are euphemistically called preservatives in food will have to be attended to; and we shall recognize the necessity for the universal employment of the aseptic instead of the antiseptic method. This will be in wise imitation of the development of surgery, and it will lead us a long way in the direction of a better thing than even aseptic surgery, and that is the disappearance of surgery and surgeons altogether."

The question of pure milk is thus seen to be intimately related to Listerism; and the dependence of surgical tuberculosis on impure milk, which is, we believe, about to be demonstrated scientifically by researches in Scotland where this disease is a veritable scourge, makes not irrational the hope that surgical tuberculosis some day may be as effectually controlled by sanitary measures as is typhoid fever.

The further chapters of the book are concerned with many topics embraced under the general subject of eugenics. Here again the author shows that he is prone to go off at a tangent; but when he keeps to the prescribed circle of his course what he has to say is both entertaining and of great practical interest. The falling birth rate, as he shows, may be combated not by increasing productiveness (which may be difficult or impossible), but by avoidance of puerperal sepsis, thus lowering the risks of motherhood, and saving from death or sterility mothers who shall give birth to still other children. The querulous objection of some that such precautions in childbirth were not necessary in the good old days, he answers by showing that in the good old days ("the *palmy* days," which as Disraeli said "had no *date*") the risks of childbirth were appalling.

Then comes a chapter on Listerism and War; and in this the author points out not only the importance of hygiene in camps, and the part which antisepsis and asepsis have played in decreasing the mortality from wounds in war; but he also proceeds to the matter of recruiting soldiers and to the difficulty which is experienced in some countries in obtaining physically fit recruits—all because Listerism as applied to childbirth, to the slums, to the public-school system, etc., has not been understood by the politician.

This is but half of the book; but the space allotted for review has already been exceeded, and we trust that the character of the volume has been indicated, and that there are many who will want to read it to the end. It is worth it. A. P. C. A.

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A Treatise on Tumors. For the Use of Physicians and Surgeons. By Arthur E. Hertzler, M.D., Assistant Professor of Surgery in the University of Kansas. Pp. 728; 538 illustrations, and 8 plates. Philadelphia and New York: Lea & Febiger, 1912.

The book is divided into three parts. The first part deals with the general biology of tumors, including discussions of the nature, classification, structure, growth, metastasis, etiology, and other important features. The second part consists of eighteen chapters dealing with the pathology of the special forms of benign and malignant tumors. This part is broadly pathological in character, but the pathological features are made subservient to the more dominant clinical phases. The third part deals with the regional consideration of tumors and is essentially clinical in character, making frequent reference, however, to the more purely scientific material of the second part. Twenty-six chapters comprise the third part, four of which are on the female genital tract, one entire chapter being devoted to carcinoma of the uterus. The book is profusely illustrated with drawings and photographs of clinical appearance, gross morbid anatomy, and pathological histology of tumors, in addition to which there are several illustrations of steps in operations indicated in the treatment. The binding is excellent, the paper heavy and glossed, and the type large and clear, divisions of the text being indicated by heavy-faced type and italics. The index is not so complete as might be desirable, there being no mention of several important conditions, notable among them being epithelioma. This is not a matter of nomenclature for the term appears in the text in various places.

From the point of view of the pathologist the book is fairly complete. It adds little if anything to the present conceptions of the etiology and general biology of tumors. Exactness of termin-

ology is not strictly adhered to, but this feature does not serve to diminish the clarity of the subject matter. The classification is simple and clear, but not sufficiently comprehensive in the subdivisions. There is too little stress laid on the subdivision of the epithelial tumors and the consideration of the various types of malignant epithelial tumors is incomplete, in so far as the histological types are concerned. In this group the important benign cystic epithelioma has not been placed, nor is it found in the index. It seems unfortunate that the "vast field of experimental oncology has been entirely omitted," for there are undoubtedly many facts that have been learned that are adaptable to a broad conception of tumor biology in its relation both to the experimental worker and the practitioner. This is especially true of transmissibility, local and general immunity, and heredity. The illustrations in this division tend to be sketchy in the histological details, as for example, Figs. 15, 17, 31. There is little attention given to the finer study of highly magnified preparations.

The regional consideration of tumors presents the work in a thoroughly authoritative fashion and is worthy of the highest praise. Both physician and surgeon will find here much of interest and instruction, for there are presented in very clear fashion the pathology, diagnosis, and treatment of the various tumors found in the given region. A clear idea is presented as to the relative frequency of the tumors considered, the differential diagnosis is discussed sufficiently and a very detailed description of the modes of treatment indicated. Important operations are described and illustrated and some of the plates, notably that showing the lymphatics of the neck are exceptionally good. The illustrations descriptive of the clinical phases of the tumors are excellent and are splendidly correlated with gross morbid anatomical and histological photographs and drawings. The literature in this division of the book has been brought up to date much more carefully than that of the part on tumors in general.

On the whole the book may be said to be of value to the laboratory man chiefly as it brings him in touch with the views of the practical surgeon; but for the general practitioner, the student of surgical pathology, the active surgeon, it must prove of great interest and worth. H. T. K.

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LABORATORY MANUAL OF PHYSIOLOGY. By FREDERICK C. BUSCH, B.S., M.D. Second edition; pp. 212; 46 illustrations. New York: William Wood & Co., 1911.

THERE is no field in the medical sciences in which a good book is so necessary as in that of practical physiology. The unsettled

and different attitudes of the various teachers of this branch is difficult to meet. What is considered of great importance by one is given a subsidiary position by another. Therefore the fact that this book, under these difficulties, has reached its second edition justifies attention and favorable consideration. The author covers the whole subject in a general way, starting with experiments of a fundamental nature and extending these to include phenomena of an applied nature. His purpose is to give a fundamental knowledge of the subject to the general student, and at the same time to make the exercises have a practical value to the student of medicine. Although one may wish for a greater and more thorough consideration of the latter side of the subject, nevertheless it is impossible in many laboratories with their limited available equipment. The author has succeeded in giving us a book that can be generally used. The instruments with which the student must become acquainted are described in a simple and lucid manner, and the diagrams are valuable. The book is sufficiently illustrated, and the exercises clearly described. In all, the book is a valuable addition to those already existing and has many advantages.

E. L.

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PATHOLOGISCHE ANATOMIE: EIN LEHRBUCH FÜR STUDIERENDE UND AERZTE. Herausgegeben von L. ASCHOFF. Second Edition. Volume I: General Etiology and Pathology. Pp. 778; 419 illustrations, many of which are colored. Volume II: Special Pathology. Pp. 997; 655 illustrations, many in colors, and 1 lithographed plate. Jena: Gustav Fischer, 1911.

THE fact that this book in the short space of two years appears in a second edition is sufficient evidence of its wide popularity. Its merit is unquestionable and its scope is so great that a detailed review seems advisable.

The extensive alterations found in text, arrangement, and illustration make for vast improvement in the work and in its present form the book is practically a new entrant in a field where its excellence alone is sufficient reason for its being. Assuming that the reader has some familiarity with the first edition, it is sufficient to point out the principal changes made in the second edition.

The chapter on exogenous causes of disease, which in the first edition was the last work of Albrecht, has been somewhat rearranged and enlarged by R. Rössle, the enlargement being most noticeable in the latter's comprehensive discussion of heredity and heritable conditions. Askanazy, in rewriting the chapter on exogenous causes of disease, has retained the form of his original contribution, but has added numerous valuable illustrations, the colored drawings

of the ova of many of the metazoan parasites being of especial value in rendering the text additionally instructive. Following these chapters an entirely new chapter by Rössle, on the general pathology of the cell, has been inserted. This is a brief but intensely thoughtful consideration of the morphological, physical, and chemical organization of the cell in its normal and pathological conditions; it serves an extremely useful purpose in elucidating the retrogressive cell phenomena. Schwalbe's chapter on malformations and monsters has been altered so little as to need no comment.

Gierke's chapter on metabolism has been increased in text and illustration, and the writer presents his subject with increasing breadth of view. As in the first edition, however, he permits the pathological conceptions to outweigh all others, and waving aside the wider considerations of metabolism as a complex process in the entire organism, deals chiefly with the morphological changes which result from altered nutrition and metabolism of the individual cell or organ.

Dietrich's chapter on circulation has been enlarged by an increased elaborateness of discussion of the circulation in its general aspect, of the disturbances of lymphatic circulation, and of embolism and metastasis. He clings to Cohnheim's conception of end arteries, and continues to accept the old Weigert distinction between hemorrhagic and anemic infarction.

In the first edition Kretz presented the subject of immunity in eight pages. He has rewritten and enlarged this chapter so that the subject matter, much of which is printed in fine type, now occupies thirty-one pages. Brief as is its present form, the chapter gives a clear discussion of the condition of infection, the pathogenesis of infectious diseases, and the nature of immunity. The descriptive sections on serum therapy, bacteriolysis, agglutination, precipitation, anaphylaxis (hypersusceptibility), cytotoxins, and phagocytosis (including opsonins) individually are good, but, as indicated, are arranged in an illogical and unnecessarily confusing sequence. Following these sections, the theory of immunity receives conventional discussion and is illustrated with the usual diagrams of Ehrlich's side-chain theory.

Lubarsch's chapter on inflammation can be dismissed with the simple statement that only slight alterations have been made, the article preserving its original clearness, authority, and breadth of view.

Borst, in his chapter on pathological growth, has considerably elaborated the discussion of metaplasia, and has written a section on transplantation, which is so much more complete and comprehensive than that of the first edition that it essentially is a new presentation. The same writer also has revised his chapter on tumors, including in the new edition an excellent discussion of

experimental work on tumors and a splendid *resume* of the present knowledge of the nature of tumors, which has been acquired by experimental research. Except for a slight change in the position of adamantinoma, the classification remains the same as in the old edition.

The sense of proportion and balance displayed in the book is splendidly maintained throughout, the only possible exception to this statement being the brevity of the chapter on immunity. It would seem that the rapid growth and increasing importance of this subject demands more attention both from pathologist and bacteriologist than even the enlarged chapter by Kretz, gives it. Granting this, however, it will be seen that this edition lays new claim to the position which Aschoff's book, from its first appearance, took as one of the leading German works in general pathology. Its excellent artizanship, its logical arrangement, its judicious illustration, its careful, clear, and painstaking treatment of the wide variety of subjects necessary in such a work, make its recommendation a duty and pleasure.

In addition to an enlargement and revision quite in keeping with that seen in the volume on general pathology, the volume on special pathology shows numerous changes in arrangement. In the present form of the book the chapters on nervous system, urinary apparatus, and genitalia follow one another in the order named, but appear between the chapters on respiration and gastro-intestinal tract; the chapter on the thymus body is retained, but the hypophysis, which was discussed in an appendix to the chapter on nervous diseases, now is included in the chapter on glands of internal secretion. All the chapters have a bibliography appended, a feature much missed in the first edition.

Aschoff has rewritten and enlarged his chapter on heart and pericardium, has elaborated the discussion on pathological physiology of the heart, and now gives a clear but brief exposition of the alterations in rhythm and association which follow disturbances of the cardiac transmission tracts. Benda's chapter on the vessels shows the beneficial effect of much careful rewriting, rearrangement, and additional illustration, and is advantageously enlarged by new and complete sections on veins and lymphatic vessels. Schridde, in the chapter on the blood-forming organs, has enlarged the sections on Hodgkin's disease and on the "myeloses." It is gratifying to see his increasing appreciation of the interrelation between the outspoken leukemias and similar aleukemic conditions. Naegli's chapter on the blood remains much as it appeared in the first edition, except for elaboration of the sections on the various forms of anemia and leukemia.

O. Naegeli's chapter on the thymus is enlarged, and the subject is presented clearly and concisely, but his personal views are emphasized even more dogmatically than in the older edition.

M. B. Schmidt has retained much of the form and text of his interesting and well-written chapter on the organs of motion (bones, joints, muscles, etc.) and has added an instructive section on the permanent alterations in the skeleton resulting from congenital and acquired pathological conditions.

Beitzke's chapter on the organs of respiration shows a more complete consideration of the diseases of the bronchi and a more elaborate discussion of the inflammatory processes in the lungs than appeared in the first edition.

The changes in P. Ernst's chapter on the nervous system are slight and hardly worthy of description.

Aschoff, in the chapter on the urinary apparatus, now divides chronic kidney affections into three instead of two groups—chronic tubulo-glomerular nephritis, chronic regenerative nephritis, and chronic kidney alteration the result of altered circulatory conditions.

M. Simmonds, in rewriting and enlarging his chapter on the male genitalia, has added several new illustrations, and has included in the text a new and valuable section on the pathology of the male urethra. Aschoff has rewritten the chapter on female genitalia so as to enlarge it and make it of distinctly greater value.

Almost certainly the most gratifying change is found in the chapter on the gastro-intestinal tract. In the first edition this was covered in a somewhat perfunctory fashion by Bernh. Fischer, but in the second edition has been taken over by Aschoff. The latter, although adhering to the original plan of Fischer, has entirely rewritten and greatly elaborated all the sections; he has added a section on hernia, and has made the chapter a splendidly written, well illustrated exposition of the pathology of this system. C. Sternberg has made very little change in his chapter on liver, bile passages, and pancreas.

Von Gierke, in the chapter on glands of internal secretion, markedly improves his chapter by a greater elaborateness of discussion of the normal and pathological physiology of the various glands.

Jores, in the chapter on skin, has made only minor changes in text and nomenclature.

It will readily be seen that the entire book has received alterations which distinctly increase its value. It deserves the same high praise that is bestowed on the volume on general pathology. It is difficult to understand the unfortunate sequence of chapters which has been mentioned above; and there is no clear reason why the thymus should not be included with the ductless glands, especially when one observes the statement of Naegeli himself that this gland is not lymphatic in character, nor does it have any blood-forming function, being in his opinion a gland purely of internal secretion. Putting aside these more or less academic considerations, the fact remains that the book is well balanced and well

written, it shows an admirable attempt to break away from purely morphological descriptions, shows a spirit of deep philosophy, is a safe guide and authoritative text-book, and in common with the volume on general pathology should continue to hold an extremely high place in the scientific literature of the world. H. T. K.

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Die Störungen des Verdauungsapparates als Ursache und Folge anderer Erkrankungen (The Disturbances of the Digestive Apparatus as the Cause and Conseauence of Other Diseases). By Dr. von Hans Herz, in Breslau. Second edition. Part I. The Blood, Metabolic and Constitutional Diseases in their Relation to the Digestive Apparatus. Pp. 218. Berlin: S. Karger, 1912.

With this volume begins the publication of the second edition of Herz's comprehensive correlative work on the disturbances of digestion, and the statement is made on the cover of Part I that the further numbers will appear in quick sequence. As far as the writer is aware, there have been no English translations of this work, the first edition of which appeared in 1898.

To wide readers of foreign literature or to European workers it doubtless needs no introduction, but to the American medical public the work is probably but little known.

To pass final judgment upon the present edition as a whole from the first section now at hand, would be premature, but a review of Part I suggests that no radical departure is to be made in this edition from the plan and scope of its predecessor. The title of the work reveals what an almost limitless field Herz has attempted to cover, and how nearly impossible of success such an effort must be in our present state of knowledge. That a single author should compass the multitudinous relations implied is bold enough, but is, perhaps, less remarkable than that he should be able to present them with brevity. It is plain that this could be accomplished only by necessary sacrifices here and there, but Herz has succeeded, nevertheless, in presenting an enormous array of curious, commonplace, and rare facts of a practical and very real interest.

The plan of the work consists in presenting and considering at length, under their respective headings of the various diseases of other organs, those disturbances of digestion which may occur as the causes, complications, or sequelæ of these conditions. In his discussion of these factors, the author presents the views of leading workers in a given line, less by a statistical summary of what has been done than by a rather happy personal style of exposition which holds the readers' attention. There is given here, of course, much play for individual opinion, of which Herz stands in no

lack, but he seems to have kept a dispassionate outlook in the midst of much controversial evidence, frequently leaving the issue frankly undecided. In other cases, however, he does not hesitate to offer conclusions as when, under gout, he states that until further evidence is forthcoming, we can in general, regard digestive disturbances in this condition as an expression of the gout itself.

The advance of medicine since the publication of the last edition of this work has been so considerable as to necessitate, evidently, not only the rewriting of most parts, but also the composition of many new one, evidence of which is clear in the table of contents and the rearrangement of its sections. Tetany, for example, has come in for a share of attention which the activity of workers in that line has of late years drawn upon it. In a consideration of its etiological factors, Herz takes occasion here, as elsewhere, to indicate his own attitude. He leans away from the view which would make gastro-intestinal toxins in the circulating blood factors of direct injury to the parathyroid glands, and espouses instead the intering but fancifully elaborated hypothesis of which Falta, Eppinger, and Rudinger are the sponsors.

The field of usefulness of a work such as this lies, of course, in many directions, but it must extend chiefly to the clinician who concerns himself with a philosophical view of medicine or the more abstract research worker who may enter the clinical realm The book is not one from which the practical physician may expect much help, except in the study of obstruse problems within its sphere, but it should be of much interest to any intelligent reader of medicine, and a store-house of information to the clinical investigator.

The paper on which the work is printed is rather heavy, but the type, as in most German texts, is excellent. A fairly extensive bibliography accompanies Part I. R. P.

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CESAREAN SECTION IN GREAT BRITAIN AND IRELAND. By ARMAND ROUTH, M.D., F.R.C.P. Obstetric Physician to Charing Cross Hospital, London; and Consulting Physician to Samaritan Free Hospital for Women, London, etc. Pp. 233. London: Sherratt & Hughes, 1911.

THIS book is the enlargement of a report read at the international Congress in St. Petersburg, 1910, and contains tables of 1282 cases of Cesarean section by over 100 British obstetricians and gynecologists living on June 1, 1910. It is designed to present a complete statement of British work done in Cesarean section. Cases of hysterotomy and hysterectomy performed before fetal viability, and cases of ruptured uterus have been excluded.

Routh introduces before his tables a historical sketch of the various operations which preceded Cesarean section, and also the modern operations which compete with it.

In treating of the history of Cesarean section in Great Britain, he quotes Playfair's statement in 1866 that the mortality was then 89 per cent. The mortality of Cesarean section has steadily diminished from 38 per cent. in 1891 and 1896; 20 per cent. in 1902; about 12 per cent. in 1904, until at the time of writing the operation has scarcely any morbidity, and a mortality under favorable conditions of 2.9 per cent.

In 1906, 90 cases for contracted pelvis are reported with a mortality of 2.2 per cent.; in 1908, 154 cases with a mortality of 4.5 per cent.

Routh brings up the interesting question of Cesarean section in septic cases, and draws attention to the familiar fact that repeated examinations and efforts to deliver with forceps increase the mortality three-fold. Likewise the rupture of the membranes before operations increases the mortality nearly five times.

He draws attention to Maxwell's recommendation that the amniotic cavity be irrigated with normal salt solution or boric acid solution, at a temperature of 100° F. before Cesarean section is performed. This may be accomplished by passing a soft metal, pliable tube into the uterus.

Where the parturient canal is probably infected, and the fetal heart weak, or the child deformed or injured, craniotomy with intrauterine irrigation is indicated; where the uterus is evidently infected, hysterectomy with intraperitoneal treatment of the stump. Thus in 216 cases infected before operation, the maternal mortality was 27.7 per cent. with the classic Cesarean section; while in 14 cases infected, treated by hysterectomy with intraperitoneal treatment of the stump, there was no maternal mortality.

In contracted pelves, British obstetricians induce labor at the thirty-fifth week for moderate contraction, with the fetus of proportionate size. If the patient is first seen at full term or labor, with no attempts to deliver, conservative section would be chosen, and in infected cases hysterectomy.

In pregnancy complicated by fibroids the patient should go to term, with section if required. In cancer, patients seen early, should have total hysterectomy, if the case is favorable for operation. If unfavorable, the patient should go as nearly as possible to full term and be delivered by section.

In ovarian tumors complicating pregnancy, it is safest to remove the tumor as early as possible. In cases seen at labor, if the tumor is abdominal, vaginal delivery should be practised with ovariotomy later. If conditions are unfavorable, removal of the tumor and section are best.

Where other pelvic tumors, retroflexion of the uterus, or stenosis are present, section has a legitimate field.

It is thought that in concealed accidental hemorrhage abdominal Cesarean section may be done in the interest of the mother. In placenta prævia, section is limited to rigid undilatable cervix, with mother and child in good condition. In eclampsia, with the patient getting steadily worse and the cervix undilatable, abdominal Cesarean section may be employed.

Vaginal Cesarean section is not a favorite operation in Great Britain.

At the time of writing, it is estimated that Cesarean section by all operators, from all indications in the United Kingdom, has a maternal mortality of 8.1 per cent. In contracted pelves the mortality with all operators was 6.1 per cent., and when favorable cases were selected was 2.9 per cent.

This interesting and valuable collection of cases will prove of great service to obstetricians throughout the world in determining the true place for the important operation of delivery by abdominal section. E. P. D.

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A MOTHER'S GUIDE. A MANUAL FOR THE GUIDANCE OF MOTHERS AND NURSES. By FRANCIS TWEDDELL, M.D., Alumnus Bellevue Hospital, New York; Fellow of the New York Academy of Medicine; Assistant Physician to the Babies' Hospital Dispensary, New York. Pp. 183; 10 illustrations. New York: James T. Dougherty, 1911.

THE author's statement, in his preface, that he aims "to give simple, clear, and complete directions, especially as regards nursing and artificial feeding of infants, and disorders of digestion," is well borne out by a perusal of his book. This little work will undoubtedly prove to be a great help to physician, nurse, and mother.

The physician will find it useful as a source of reference to which the mother can be directed for specific information as to how to carry out his orders, such as for pasteurization, sterilization, peptonization of milk, preparation of whey, barley water, beef juice, etc. To the nurse it will be a ready reference book when memory fails.

An intelligent mother, who grasps the thought of the book and so acquires a rational outlook on the problems of infant life, will be well repaid for the time spent in its study. As a guide to how to keep a healthy baby well it leaves nothing to be desired.

The advisability of including the section on acute infections is doubtful, especially as treatment is outlined. The symptoms of graver import are, however, described and if the frequent admonition to call in the family physician is not disregarded, while this treatment is tried, it may serve a useful purpose. A. A. H.

OPHTHALMIC MYOLOGY. A SYSTEMATIC TREATISE ON THE OCULAR MUSCLES. By G. C. SAVAGE, M.D., Professor of Ophthalmology (Defects of the Eye) in the Medical Department of Vanderbilt University. Second edition; pp. 685; 84 illustrations and 6 plates. Nashville: Published by the Author; printed by McQuiddy Printing Company, 1911.

As the law of monocular and binocular rest and motion, as also the law of direction, is based upon the recognition of the true locations of the posterior and anterior poles of the eye, the author insists that Helmholtz's work is vitiated by two fundamental errors: (1) In not taking the centre of the macula as the posterior pole, and (2), in holding that visual lines are axial rays instead of prolonged radii of retinal curvature. He also thinks that Listing's law is not true, but "should be forgotten in the interest of truth." The writer posits a number of innervation centres, not upon the basis of anatomical localization, which he considers necessary to explain the phenomena of ocular movements.

In the practical portion of the work adequate space and consideration is given to the various anomalies of the ocular muscles. Cyclophoria, which is in large measure peculiarly the writer's own domain, is perhaps more fully treated than in any other work dealing with this subject. Numerous apposite clinical cases are cited in illustration of the principles laid down. Among the former, it may be worth while to call attention to the report of a case in which an eye with good vision was enucleated, but not by the author, to relieve severe nervous symptoms caused by what was considered hopeless muscle imbalance. The operation is said to have cured the patient—a truce to comments! T. B. S.

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MANUAL OF PRACTICAL PHYSIOLOGY. By JOHN C. HEMMETER, M.D., Ph.D., LL.D. Pp. 223; 55 illustrations. Philadelphia: P. B. Blakeston's Son & Co., 1912.

THE practical physiology of Hemmeter is the product of the long experience of the teacher and no doubt, in the hands of his students, is of great value. The instruments described are in a large measure those of Porter, from whom he liberally contributes in describing them. He takes up in an elementary manner, muscle and electrophysiology. In like manner he considers blood and circulation. Respiration receives scant attention as does vision and digestion. The internal secretions, however, are given considerable space and the chapter devoted to this subject is very satisfactory. Immunity is also referred to. The text is clearly written in simple language which, no doubt, can be readily understood by the student. E. L.

# PROGRESS

OF

# MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF

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**The Successful Inoculation of Blood, Blood Serum, and Sperm of Syphilitics into Rabbits.**—P. UHLENHUTH and P. MULZER (*Berl. klin. Woch.*, 1912, xlix, 152) have succeeded in inoculating rabbits with the blood, blood serum, and sperm of syphilitics. The defibrinated blood of a woman with secondary lues (only a few papules on the buttocks) was obtained from an arm vein. On dark field examination, no spirochetes could be demonstrated. Into the testicles of each of three rabbits, 2 c.c. of blood was injected. All three animals developed a syphilitic orchitis with enormous numbers of active spirochetes in the lesions. The first lesion appeared just eight weeks after inoculation. From a man with florid syphilis, a recurrence following salvarsan treatment, defibrinated blood and blood serum were obtained and were similarly injected into the testicles of rabbits. From the same patient sperm was secured by manual friction. The penis and glans were free from visible lesions. They were thoroughly cleansed and the sperm, received in a sterile Petri dish, was immediately diluted with about one-half volume of lukewarm salt solution. One cubic centimeter of this mixture was injected into each testicle of three rabbits. The sperm showed actively motile spermatozoa, no red blood corpuscles or pus cells. Neither blood, blood serum, nor sperm showed spirochetes on examination with dark field illumination. Blood and blood serum each gave two positive inoculations out of three trials, while with sperm all three animals inoculated developed syphilitic orchitis. Uhlenhuth and Mulzer suggest the bearing of these experiments on hereditary lues and on the diagnosis of obscure cases with negative Wassermann reaction. The inoculation method opens wide possibilities which are being investigated by Uhlenhuth and Mulzer.

**An Epidemic of Sore Throat Due to a Peculiar Streptococcus.**—D. J. Davis and E. C. Rosenow (*Jour. Amer. Med. Assoc.*, 1912, lviii, 773) state that during the last three months in Chicago, there has been an epidemic of sore throat characterized by unusual severity, and with complications strikingly different from those of other years. A streptococcus with certain features is found in practically all cases. The attack begins suddenly with or without chill. Fever and constitutional symptoms are out of all proportion to the local involvement. The throat presents a diffuse redness. The tonsils are always infected, the crypts filled with exudate. A grayish membrane may spread over a large part of the tonsil with only occasional ulceration. The acute symptoms often subside in a few days. But at the end of a week, the patient may suddenly become worse with a clinical picture suggesting septicemia. The cervical glands may become very large, but usually do not suppurate. Otitis media is frequent. Empyema, erysipelas, meningitis, etc., are found as complications, most often in the group of cases with little glandular involvement but marked constitutional reaction. Blood cultures are usually negative. A pure streptococcus can be grown in practically all cases, from the tonsils and secondary lesions indicated; it is Gram-positive, capsulated, occurring in short chains and pairs. Culturally it appears to occupy a position between Streptococcus pyogenes and mucosus capsulatus. It is not the pneumococcus. Passage through animals, to all of which the organism is highly virulent, increases the capsular substance strikingly. From this characteristic, and from the fact that the capsule is lost on artificial media, Davis and Rosenow suggest that the capsule and high virulence are the results of frequent human passage, which may explain the unusual tendency to complications, and the general severity of the disease.

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**Pericarditis in Bright's Disease; Its Relation to Nitrogen Retention.**—F. Widal and A. Weill (*Jour. Urologie*, 1912, i, 177) observe that pericarditis has long been recognized as a complication of chronic nephritis. Bright believed its frequency due to chemical alteration of the blood. A review of more recent literature shows varying opinions as to its cause. Widal and Weill have studied 11 cases, 7 recognized during life. All showed high nitrogen content of the blood serum, 5 cases having 1.87 gram and 1.95 gram per liter, 6 between 2.3 grams, 3 over 3 grams. In 4 cases, cultures from the pericardium showed no growth, 2 cases showed Bacillus coli which did not, however, agglutinate the patients' serum collected ante mortem, 1 showed streptococcus, and 4 pneumococcus, 2 of which had concomitant pneumonia. From these and similar observations, Widal and Weill believe that pericarditis in Bright's disease is a manifestation of marked nitrogen retention, of equal importance on this account as for its localization.

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**The Relative Value of Immediate and Delayed Laparotomy in Pneumococcal Peritonitis.**—To attempt to estimate the effect of immediate laparotomy in pneumococcal peritonitis, H. C. Cameron (*Proc. Roy. Soc. Med.*, 1912, v, Clinical section, 123) has analyzed the cases admitted to Guy's Hospital during the last nine years. Of the 19 female cases, 15 occurred between the ages of five to fifteen

years; of the 7 male, all were aged under twenty-two years. The disease is an acute peritonitis due to a pneumococcus septicemia, characterized in addition by the great and rapid exudation of fluid into the peritoneal cavity. The diagnosis is suggested by the patient's age and sex; by an onset with rigors, convulsions, or herpes labialis; by the early appearance of delirium or pronounced diarrhea; by the simultaneous presence of pleurisy, pericarditis, or pneumonia. The course is a two or three weeks' fever, suggesting typhoid, but with more intense abdominal symptoms. At the end may be left a residual collection of pus, often sub-diaphragmatic, sometimes more diffuse, forming with greater rapidity than in tuberculous peritonitis. In those who pass successfully through the septicemia, recovery may take place. A minority of cases die as a result of failure of drainage of residual pus collections. Cameron believes that there is no evidence that laparotomy at the onset increases the chances of recovery from the septicemia, or helps to cut short the process in the peritoneal cavity. So it is wiser to delay operation until the disease has become localized in the peritoneum, just as is done in dealing with the empyema following pneumonia.

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**The Relation of Chorea to Rheumatism; An Analysis of 300 Cases.**—M. S. FRASER (*Practitioner*, 1912, lxxxviii, 461). The object of this paper is to discuss the clinical evidence in regard to the relation of chorea to rheumatism. From his analysis, Fraser finds that 53 per cent. of his series showed definite evidence of rheumatism either previously to or concurrent with the attack of chorea; 72 per cent. had either a personal or strong family history of rheumatism. In a large number there was a history of nervous diseases in other members of the family. In comparing the age incidence, Fraser, agreeing with Guthrie's figures, found a marked increase in chorea between six to twelve years, and in acute rheumatism between seven to twelve years. The seasonal incidence, agreeing with Gabbet, showed the maximum of chorea one month later than rheumatism. According to Batten, 25 per cent. of 115 chorea patients treated at the time, without signs of rheumatism, developed it within six years. In regard to the relation of previous disease, Fraser's figures showed that measles and whooping cough had no connection with the onset of chorea. Neither scarlet fever nor diphtheria seemed of any appreciable importance. Hence, Fraser believes that the majority of choreas are closely associated with rheumatism, and that possibly all cases of true chorea are rheumatic in origin, with chorea a cerebral manifestation.

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**The Causes of Death in Tabes.**—CHARLES W. BURR (*Jour. Nerv. and Ment. Dis.*, 1912, xxxix, 145) finds that persons suffering from chronic degenerative diseases of the spinal cord do not, as a rule, die from them, but from some general affection attacking other organs. This is typically true of tabes, though sometimes the disease may be indirectly the cause of death. The observation of accompanying lesions is of practical therapeutic importance, since treating them may lead to prolongation of a life bearable for the patients. To emphasize the necessity of thorough diagnosis, Burr gives the protocols of 34 cases. General arteriosclerosis is so common as to be regarded as part of the

morbid anatomy of tabes. Chronic myocarditis, valvular heart disease, and chronic nephritis were noted most frequently. Aneurysm was found in 3 cases, not causing death; 6 died from pulmonary tuberculosis; 5 from croupous pneumonia; 2 from septicemia from bedsores. In conclusion, Burr considers his figures are of no value save to show that death in tabes may come from some complication early, or may be delayed for many years. So the life of a tabetic is not definitely limited. It may be long or short, the disease not progressing evenly.

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**The Value of the Antigen Reaction of Debré and Paraf for Rapid Diagnosis of Urinary Tuberculosis.**—M. CHEVASSU (*Presse Méd.*, February 28, 1912, xvii, 173). Debré and Paraf have used for diagnosis of renal tuberculosis a modification of the Bordet-Gengou reaction. In a suspected case they have used for antigen the patient's urine, for antibody, known tuberculosis serum, and have tested the deviation of complement against a hemolytic system of sheeps' corpuscles and anti-sheep serum. Chevassu reports with this method a series of 29 cases controlled by autopsy or operation, 15 cases controlled by guinea-pig inoculation, and 36 cases not controlled save by clinical observation. Little stress is laid on the last. Chevassu finds that this reaction gives exact results in nine-tenths of the cases. In none was a negative reaction obtained with a positive control. On the whole, Chevassu concludes that this method is of great value for the rapid positive diagnosis of renal tuberculosis, but of greater value negatively. For the failure to find organisms in urine has never been significant, and a negative inoculation is far less convincing than a positive.

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**On the Lesions Produced in the Appendix by Oxyuris Vermicularis and Trichocephalus Trichiura.**—From reviewing the literature, R. L. CECIL and K. BULKLEY (*Jour. Exper. Med.*, March, 1912, xv, 225) find that of parasites observed in the appendix the most common are oxyuris and trichocephalus, but that there has been slight effort to determine whether their presence is fortuitous, a predisposing factor for disease, or the existing cause of it. They have therefore studied 148 unselected appendices of children between the ages of two and fifteen years to determine the frequency of incidence of parasites, the percentage of cases in which specific lesions could be demonstrated, and the character of each. Oxyuris was found more commonly. The series of controls was so small that no definite conclusions could be drawn, but Cecil and Bulkley believe that as 7 per cent. of healthy children, according to Schloss, have oxyuris, such a percentage or less would probably represent its incidence in the normal appendix of children. In disease, the pathological picture seemed characteristic. Grossly the organ is moderately swollen and rigid, the lumen filled with blood and mucus. The mucosa is swollen and more velvety than normal. In most cases, in the neighborhood of the parasite are usually purpuric spots or small hemorrhagic ulcers. There is no suppuration, gangrene, or perforation. Microscopically, where the oxyuris has invaded the mucosa, but with little destruction of tissue, there is extensive extravasation of blood through the ruptured epithelium into the lumen, but without inflammatory reaction. In more marked cases

there is necrosis of the mucosa, with formation of ulcers characterized by hemorrhagic bases, undermined edges, and no reaction save with secondary infection. The process may heal with encapsulation of the worm. Hence they conclude that oxyuris in a diseased appendix may produce characteristic lesions, and in most cases is the exciting cause of the pathological changes found. The trichocephalus cases were few. These parasites show a tendency to burrow along beneath the columnar epithelium in contrast to the oxyuris, which penetrates more deeply. Otherwise the picture is not distinctive.

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**The Avoidance of Anaphylactic Phenomena on the Injection of Immune Serum.**—E. FRIEDBERGER and S. MITA (*Deut. med. Woch.*, 1912, xxxviii, 204) review the various methods which have been proposed for the prevention of serum disease, of which Besredka's is the best. An experiment of Bordet's suggested to Friedberger and Mita a new procedure which they have tested experimentally on guinea-pigs. The animals were first sensitized to horse serum and then the fatal dose of serum when injected intravenously was determined. The remaining animals were given varying amounts of serum, *i. e.*, one or more times the fatal dose, all injections being intravenous. It was found that when the serum was injected very slowly eighteen to sixty minutes), as much as ten times the fatal dose could be administered safely. Friedberger and Mita believe their results warrant trial of their method by clinicians when it becomes necessary to re-inject an individual with the same kind of serum or in cases where hypersusceptibility is suspected.

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**Urobilin and Bilirubin in Human Blood Serum.**—O. ROTH and E. HERZFELD (*Deut. med. Woch.*, 1911, xxxvii, 2129) have examined the sera of more than 80 patients, many with marked urobilinuria, for the presence of urobilin and urobilinogen, using the zinc acetate and Ehrlich's aldehyde reactions, respectively. All results have been negative. On adding urobilin to serum, it may be readily detected in this manner. But when a few red blood corpuscles are present in the serun the test for urobilin quickly disappears if the mixture be shaken a few minutes, suggesting that the urobilin has been oxidized. Next, they treated alcoholic solutions of urobilin with nascent oxygen and with carbon dioxide and found that oxygen causes a disappearance of the urobilin, whereas carbon dioxide is without effect. They now added urobilin to two portions of defibrinated blood; the one was shaken in the air and urobilin quickly disappeared, while the other, previously saturated with carbon dioxide, showed no loss in urobilin. If oxidation explains the absence of the pigment in the blood serum, it should be possible, by reduction, to demonstrate urobilin in the serum of patients with marked urobilinuria. By the addition of zinc to such serum, urobilin was demonstrable, but the results were not constant, as in the oxidation experiments. A single experiment with a piece of fresh rabbit's kidney in place of the zinc gave a positive result, but there has been no opportunity to repeat this. The reported presence of urobilin in the serum of fatal cases of pneumonia they attribute to possible lowering of oxidation in the body. Practically all patients gave positive, though often weak, reactions for bilirubin in the serum.

**On the Determination of Urea in the Urine.**—O. FOLIN (*Jour. Biol. Chem.*, 1912, xi, 507) describes a new method for determination of urea in the urine. "The urine is diluted so that 1 c.c. contains 0.75 to 1.5 mgms. of urea nitrogen. Dilutions of 1 in 20, 1 in 10, or rarely 1 in 5 are usually adequate for this purpose. One cubic centimeter of the diluted urine is then transferred by means of an Ostwald pipette to a large Jena test tube (2000 mm. by 20 mm.) previously charged with 7 grams of dry potassium acetate (*free from lumps*, 1 c.c. of 50 per cent. acetic acid, a small sand pebble, or better, a little powdered zinc (not zinc dust) to prevent bumping during the boiling, and a temperature indicator. The test tube is then closed by means of a rubber stopper carrying an empty narrow 'calcium chloride' tube (without bulb) as a condenser (size of calcium chloride tube, 25 cm. by 1.5 cm.). The test tube and condenser are then suspended by a curette clamp so that it can be easily raised or lowered with reference to the small flame of the micro-burner. As soon as the acetate is dissolved and the mixture begins to boil, which usually occurs in about two minutes, the indicator begins to melt, showing that the desired temperature (153° to 160° C.) has been reached. The boiling is continued in a gentle, even manner for ten minutes, at the end of which time the decomposition of the urea is already completed. The apparatus is removed from the flame and the contents are diluted by the addition of 5 c.c. of water. The water is added by means of a pipette through the calcium chloride tube so as to rinse the sides of the tube and the bottom of the rubber stopper from traces of ammonium acetate which may be there. Not more than 5 c.c. of water should be used for this purpose. An excess of alkali, 2 c.c. of saturated sodium hydrate or potassium carbonate solution, is added and the liberated ammonia is driven off by means of a strong air current into a 100 c.c. measuring flask containing about 35 c.c. of water and about 2 c.c. of $\frac{n}{10}$ acid. The time required for this will, of course, depend on the strength of the air current. (In Folin's laboratory ten minutes suffice.) The ammonia thus set free is determined colorimetrically against 1 mgm. of nitrogen in the form of ammonium sulphate (see total nitrogen method)". For further details, consult the original communication.

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**Painting the Peritoneum with Tincture of Iodine in Tuberculous Peritonitis.**—A. HOFMANN (*Münch. med. Woch.*, 1912, lix, 531) reports very good results in the treatment of four cases of tuberculous peritonitis—both dry and exudative. The treatment consisted in opening the peritoneal cavity evacuating fluid, if present, and painting the peritoneal surfaces of the gut and the abdominal wall with 10 per cent. tincture of iodine. Soon after the operation, the peritoneal cavity filled with exudate, but there were practically no fever and no subjective symptoms. In the course of two weeks, the exudate disappeared. The duration of treatment was about four weeks. Subsequent examination of all four cases seemed to show that they were cured. The beneficial effects of this treatment are evident at a much earlier date than with simple laparotomy. The value of the tincture of iodine is due partly to the intense hyperemia of the peritoneum, which is produced.

# SURGERY

UNDER THE CHARGE OF

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**Evidence of Occult Blood in the Stools and Stomach Contents and its Relation to the Diagnosis of Surgical Conditions of the Stomach, Especially for the Early Diagnosis of Gastric Carcinoma.**—ZOEPPRITZ (*Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1912, xxiv, 538) says that the guaiac test, properly applied, is sufficiently exact and dependable for clinical use. In stomach diseases the opportunities for demonstrating the presence of occult blood are especially favorable because not only the stools, but the stomach contents can be examined and the results in both can be compared with each other. Blood not coming from the stomach may be found in the vomit, but it is of slight importance when the proper precautions are taken against sources of error. The regular finding of occult blood is the most constant and dependable non-specific symptom of gastric carcinoma and is an early symptom of the same. It is already present when the patient seeks aid of the physician. Negative blood findings in the stool speak almost absolutely against gastric carcinoma. Regular findings of occult blood in the stools and stomach contents, in the presence of subjective stomach symptoms, speak for a probable carcinoma and indicate an exploratory laparotomy. For a recurrence of carcinoma of the stomach, the recurrence of occult blood findings is the first alarming symptom. In the very rare cases in which the gastric carcinoma does nor respond to the guaiac test this is due not to the absence of blood but probably to the presence of substances which destroy the blood pigment.

**A Contribution on the Transplantation of Bone.**—BASCHKIRZEW and PETROW (*Deut. Zeit. f. Chir.*, 1912, cxiii, 490) found by experimentation on rabbits that in free bone transplantation most of the bone pieces soon died. Some of them, which were more viable than others or met with especially favorable conditions for nourishment, remained alive a long time but they finally died of exhaustion. For the regeneration of bone transplanted in the muscle layers, the retention of the periosteum and medulla is not absolutely necessary. Resorption will proceed in a large piece of bone deprived of its periosteum and transplanted between the muscle layers, and it may heal in and be replaced by new bone tissue. The regeneration is much better in an autoplastic than in a homoplastic transplantation. The destructive process is much

less active but the bone substitution is more active and more complete. The chief source of regeneration in a piece of bone transplanted between the muscle layers, is in the young connective tissue elements which grow around the bone, pressing into the medulla, vessel spaces, and small canals and which undergo metaplasia into osteoblasts and bone cells. The covering of periosteum and endostium undergoes partial necrosis. The remaining portions may be capable of regenerating new bone, but the permanence of this production is questionable and its differentiation from that produced by the new connective tissue is often impossible. One should, therefore, assume that a covering of periosteum on the transplanted bone is an advantage. The role of the periosteal covering has not yet been explained, although it is evidently a useful one. The quicker adhesion of the transplanted bone to the surrounding tissues, the retardation of the all too rapid absorption, the early impulse toward new bone formation, are so many favorable conditions associated with the periosteal covering. A transplanted piece of bone which has healed in and has died, will not lead to bone formation after a long time. The fundamental point supported by free osteoplasty is that of the transplantation of living bone. The reaction of the surrounding tissue upon the transplanted bone varies greatly according to whether the bone is from the same patient or not, is covered with or deprived of periosteum, or is living or dead.

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**Low Position of the Transverse Colon.**—SMOLER (*Zentralbl. f. Chir.* 1912, xxxix, 417) says that there are cases in which the ptosis of one organ, although accompanied by a general enteroptosis, stands out prominently in the clinical picture. In those the replacement and fixation of this organ in its normal place, is the only treatment which can free the patient permanently of his troubles. This applies to the kidney, liver, and stomach, and a proper choice of cases will usually be followed by favorable results. Much more rarely will a ptosis of an individual loop of intestine be responsible for the clinical picture. Smoler reports such a case. A woman, aged thirty-five years, had suffered for years from pain in the abdomen which was especially frequent at night and disturbed her sleep. The patient often had the sensation of a distended transverse coil of intestine. The *x*-rays showed a high grade of ptosis of the transverse colon, which reached almost as low as the symphysis pubis. The stomach was slightly dilated. Through a median incision above the umbilicus, the transverse colon could not be seen until it was drawn up. A reef was taken in the transverse gastrocolic omentum and on one side was fixed to the round ligament by suture, on the other side to the anterior surface of the stomach. The after-course was without incident. The *x*-rays showed the transverse colon in about its physiological position. The bowel movements which before the operation required laxatives, were afterward spontaneous, and there was no disturbance of sleep. The patient now enjoys complete health.

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**Paralysis after the Use of Esmarch's Tourniquet.**—KAUSCH (*Zentralbl. f. Chir.*, 1912, xxxix, 499) says that because of the danger of consecutive paralyses, some surgeons will not employ Esmarch's tourniquet especially in the arm. Kausch believes that the paralysis can be avoided by a proper technique. He makes much use of local

anemia, but avoids it in arteriosclerosis and diabetic gangrene. He has had only 1 case which developed paralysis. In this one the tourniquet was applied much too tightly and there remained for some time after its removal a deep furrow. The circulation returned quickly in the usual manner, but at the site of the furrow there was a swelling and very painful infiltration, which disappeared only after about four weeks. The three nerves were totally paralyzed. Three months after the operation, active motion was first observed in the fingers, and six months after the operation all the muscles could be moved voluntarily, but were still weaker than on the opposite side. Not enough attention is given by the surgeon to the application of the tourniquet, which is usually left to one of the younger assistants. Kausch employs a broad bandage, 10 to 15 cm. wide. In applying it the middle is drawn tightest, the edges less. In aseptic cases the limb is made bloodless from the periphery upward, the bandage being applied weakly at first and gradually more strongly. Local foci of infection are passed over. In a case of diffuse infection, the limb is not rendered bloodless from the periphery upward, but is held vertically for ten minutes. The bandage is then applied quickly, immediately constricting all the vessels, not vein first and then arteries, because this would cause a venous hyperemia.

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**Hematuria of Nephritis and Renal Papillitis from a Surgical Standpoint: A Study of 73 Cases.**—BARRINGER (*Amer. Jour. Urol.*, 1912, viii, 229) says that in these 73 cases there was a large proportion of cases of mild toxic nephritis, probably unilateral, giving no classical symptoms of nephritis, and giving rise to or accompanied by unilateral hematuria, the hematuria being out of all proportion to the nephritis present. There was a small proportion of cases of infectious nephritis, probably unilateral, giving rise to unilateral hematuria. There was a small percentage of cases of typical toxic nephritis, giving rise to the symptoms and urinary findings of nephritis, and giving rise to hematuria, probably, as a rule, bilateral. There was an indefinite number of cases of pelvic conditions variously named varicose veins of the papilla, pyelitis cystica, metaplasia of the renal pelvis, etc., giving rise to unilateral hematuria. In a large proportion of cases these pathological conditions of the kidney pelvis or papilla are caused or accompanied by a nephritis, toxic or infectious. Hemorrhagic nephritis is most frequently confused with kidney stone, tuberculosis, and neoplasm. The differential diagnosis between hemorrhagic nephritis and neoplasm is alone considered. In the former the age is from twenty to fifty years, in the latter from forty to seventy years. In the former, tumor is absent in probably 80 per cent. of the cases, in the latter is present in 60 to 80 per cent. In the former the hematuria is constant, in the latter it is present in most cases. In the former the duration of the hematuria is from days to thirty years, in the latter if it extends into years all neoplasms but hypernephromas may be excluded. In the former the hematuria may persist for years with no tumor, in connection with the latter there is a small percentage of cases of hypernephroma where hematuria has existed for some years and in which no tumor is present. This is not so in other neoplasms. In the former the functional capacity is generally normal, in the latter generally decreased. In the former the pain or kidney tenderness is often present,

which is also true of the latter. In the former varicocele is absent, in the latter it is present in one -fourth of the cases. If there is any doubt about the symptoms, if the diseased kidney be enlarged or if the patient be a poor subject for palpation; if the function of the diseased kidney be one-half or less than that of its fellow, or if the bleeding has endured less than four years, an exploratory laparotomy for diagnosis should be done. In a majority of cases operation was primarily performed for diagnosis and not for cure of the hematuria. There is no reason for nephrotomy either to arrest hemorrhage or for diagnosis. Nephrectomy is contraindicated unless there is danger of death from hemorrhage. If the diagnosis can be made there is no indication for operative interference unless other means to stop the hematuria fail. These nonoperative means are: rest in bed; internal administration of turpentine; injection of adrenalin into the renal pelvis. Of operative methods to arrest the hemorrhage either decapsulation or pyelotomy or both seem more adequate than nephrotomy or papillotomy.

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**The Technique of Paravertebral Nerve Anesthesia.**—Finsterer (*Zentralbl. f. Chir.*, 1912, xxxix, 601) has employed this method of anesthesia in 6 laparotomies. In two colostomies, the results were negative, it being necessary to infiltrate also the deep tissues in order to complete the operation without narcosis. In the remaining 4 cases complete anesthesia was obtained. The technique is as follows: The spine of the first lumbar vertebra is first determined by palpation, when 3 to $3\frac{1}{2}$ cm. from the median line, after anesthetizing the skin, an injection needle marked in centimeters is passed vertically to a depth of 4 to 5 cm. according to the thickness of the tissue, until the transverse process is struck. The needle is then made to feel for the upper border of the process, when by carrying the syringe outward and downward the needle is made to pass inward and upward and is pushed forward $\frac{1}{2}$ to 1 cm. Five cm. of a 1 per cent. solution of novokain are then injected in a fan-shaped area. One must be careful not to push the needle too deeply when the anesthetizing fluid would be injected beyond the ganglion and be useless. The points for injection of the 1st, 2d or 3d lumbar nerves, will be at intervals of $3\frac{1}{2}$ to 4 cm. according to the size of the individual. The transverse process is to be employed as the guide as in the first injection. Of the 4 successful cases, one was a woman, aged eighty-one years, operated on for a diffuse peritonitis. In the second the patient was a cachectic man, aged forty-seven years, operated on for a chronic ileus from an inoperable carcinoma for which an ileocolostomy was done. The third case was that of a man, aged fifty-three years, with a tuberculosis of both lungs, in whom an artificial anus was made. The fourth case was that of a man, aged nineteen years, who was operated on for an acute recurring appendicitis. The method is not advised as the routine procedure in operations for appendicitis or colostomy. It should be employed when severe diseases of the lungs make a short ether narcosis dangerous and especially for the extirpation of tumors of the cecum and sigmoid flexure and for ileocolostomy, in patients who are much depressed.

# THERAPEUTICS

UNDER THE CHARGE OF

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**Calcium Salts in the Treatment of Asthma.**—KAYSER (*Therap. Monatsheft.*, 1912, xxvi, 165) has treated 13 cases of asthma and similar conditions prophylactically by calcium chloride. He gave the calcium chloride in the form of a solution containing 20 gm. of calcium chloride, 40 c.c. simple syrup, and distilled water up to 400 c.c. The patient was given a tablespoonful of this solution in milk every two hours for a period of eight days. The patients all noticed a distinct improvement; their breathing and expectoration became much easier and their sleep was not disturbed by attacks of dyspnea. In all but 2 cases no attacks of dyspnea and cough occurred after three days of treatment. In some of the cases the freedom from attacks has been permanent. Kayser explains the action of calcium chloride in asthma by its sedative action upon the nervous system and he cites its beneficial effect in other nervous affections.

**Normal Human Blood Serum Injections in Melena Neonatorum and Other Conditions.**—WELCH (*Therap. Gazette*, 1912, xxxvi, 81), drawing his conclusions from an experience with 32 cases of hemorrhagic conditions, treated by normal human blood serum, is convinced that this agent is specific in its action in controlling the bleeding. He gives the details of some of the cases he has treated and refers to a previous communication on the same subject. He does not believe that injections of defibrinated blood have any advantage over injections of serum. He says that experiments made by Ehrlich have demonstrated that the red blood cells injected into the same species call forth a hemolytic body for their digestion and removal, which he calls isolysin. In the production of the isolysins a certain amount of cellular energy is consumed which is just so much extra tax on the individual capacity for general resistance. The serum is so easily obtained that Welch can see no reason for using whole blood, especially in babies, thereby possibly reducing the strength of the child, already at the lowest ebb. Transfusion of blood is of great value, but is accompanied by certain dangers. Hemolysis, thrombosis, and embolism, all or any of which may lead to the death of the patient, are to be feared. The practical disadvantages of transfusion are, first, the difficulty of the operation which is not so simple as many suppose; secondly, it is frequently necessary to repeat the transfusion and this is a great disadvantage, while on the other hand normal blood serum can be repeated frequently and used indefinitely. However, for certain cases of very marked depletion from prolonged hemorrhage—the only measure offering any hope is transfusion.

**Camphor and Pneumococci.**—SEIBERT (*Med. Record*, 1912, lxxxi, 750) reports his results with injections of camphorated oil in pneumococcic pneumonia. He says that the injections invariably reduce the toxemia until practically normal conditions were reached three or four days after the first injections, while the alveolar exudate remained, to be absorbed later on. This phenomenon and the absence of a crisis were noticed in every case. He gave 12 c.c. of a 20 per cent. camphorated oil every twelve hours to adults and 6 c.c. to children, irrespective of the intensity of the toxemia and the extent of the local process. In a subsequent series of patients the results were apparently not so favorable. In 2 cases of severe pleural pneumonia the camphor reduced the general toxemia markedly but did not prevent a subsequent empyema. However, both these patients recovered after an operation. Two other patients had a sudden rise of temperature on the second and third days of the treatment but the camphor injections were continued and both patients recovered. This exacerbation proved to be due to pneumococcic nephritis and promptly subsided under treatment by hexamethylenamin. Of 37 cases of pneumonia so treated only one resulted fatally. This patient was a man, aged sixty-eight years, weighing 200 pounds, with a fatty heart, who had a double pneumonia with marked toxemia. The camphor injections had a good effect upon the sensorium, the temperature and the respiration, but his heart gradually failed and he died on the sixth day. Seibert also relates animal experiments with camphorated oil injections in 20 animals simultaneously inoculated with fatal doses of pneumococci. Death was prevented in 9 of the animals and retarded from two to five days in 8 more. He believes that camphor injections in human and animal pneumococcic infections materially assist in overcoming the toxemia. He found that injections of 10 c.c. of a 30 per cent. camphorated oil (equal to 36 grains of pure camphor) to 100 pounds of human body weight every eight to twelve hours are entirely harmless.

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**The Treatment of Melena Neonatorum by Human Blood Serum.**—NICHOLSON (*Therap. Gazette*, 1912, xxxvi, 77) reports a case of melena neonatorum treated by injections of normal human blood serum with complete recovery. Nicholson believes that the subcutaneous or intramuscular injections have a distinct advantage over actual transfusions for two reasons: (1) That the latter requires special skill for its performance, it being a delicate operation even in the adult and requiring special appliances; and (2) the difficulty in obtaining suitable donors. He believes that the injection of blood serum is a very practical measure and so very useful in combating emergencies.

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**Untoward Results from Transfusion of Blood in Pernicious Anemia.**—BENNECKE (*Münch. med. Woch.*, 1912, lix, 571) refers in this article to the lack of benefit resulting from intravenous injections of defibrinated blood in the treatment of pernicious anemia. The article is apparently a criticism of a number of observers who have recommended the intramuscular or subcutaneous injections of defibrinated blood for the treatment of pernicious anemia. The transfusions were used as measures of last resort in the cases reported by Bennecke usually in the terminal stages of the disease and therefore the test of even the intra-

venous injections of defibrinated blood was not entirely fair. Bennecke treated 5 cases and the treatment was followed by an increase in the hemoglobin and red blood cells in only one case. This improvement might have been explained, according to Bennecke, by a spontaneous remission of the disease. Bennecke believes that the injections are not entirely without danger and he thinks that death was hastened by them in one case at least.

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**Vaccine Therapy in Rheumatoid Arthritis.**—HORDER (*Lancet*, 1912, clxxxii, 1053) says that in every case of rheumatoid arthritis careful investigation should be made to determine any possible focus of local infection. The mouth should be carefully investigated, also the fauces, the nose, the naso-pharynx, nasal sinuses, the respiratory tract, the small and large intestine, the urinary tract, and the uterus. Any lesion in one or more of these situations should be investigated bacteriologically. If any infective focus is found, there must be evidence of a causal connection between the predominating organism and the arthritis. Before beginning vaccine treatment the focus of infection must be treated locally. It must be drained or subjected to the necessary surgical measures for its eradication. Horder says that, in actual practice, the microörganism most often found as the infective element of the disease is a type of streptococcus, not streptococcus pyogenes; but streptococcus salivarius or streptococcus fecalis, streptococci of relatively low virulence, not tending to suppuration and traceable, as the name suggests, to the mouth or intestine. Other microörganisms are much less common; the gonococcus, pneumococcus and the colon bacillus, have also been found by competent observers. Possibly Staphylococcus aureus or albus, influenza bacillus, and certain bacilli related to the diphtheria bacillus may be included in this list of bacteria. The initial dose of vaccines should be small and the dosage should be very gradually increased. Horder recommends the vaccine treatment especially for chronic cases and it should be continued for at least three months before definite conclusions can be drawn as to its results. He says that of course organic changes in the joints cannot be influenced by the treatment, but that many cases seem to change from an active to a quiescent stage and a few appear to be entirely arrested. The vaccine treatment should be discontinued upon the occurrence of increase in pain, stiffness or swelling of the joints, loss of weight, or nervous disturbances.

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**Subcutaneous Injection of Small Quantities of Human Blood in Spontaneous Hemorrhage of Newborn.**—MEYERS (*Arch. of Pediatrics*, 1912, xxix, 197) relates the history of a child who, when thirty-two hours old, had repeated stools composed entirely of tarry blood clots. The hemorrhage from the bowels was accompanied by the vomiting of considerable quantities of clotted blood. At the end of twenty-four hours of this repeated bleeding the child's condition seemed practically hopeless. The weight had fallen to four pounds and eight ounces and the skin and mucous membranes were almost bloodless. Meyers injected into the subcutaneous tissues of the baby's buttock 3 c.c. of blood withdrawn from a vein of the mother's arm. The injection was made quickly so that the blood could not coagulate. A slight hemor-

rhage from the bowels occurred two and one-half hours after this injection. A second injection of 5 c.c. of maternal blood was given about five hours later. After this injection the bleeding was not repeated and the child's nutrition rapidly improved. The blood injected was quickly absorbed and a few hours afterward the site of the injection could be recognized only by the needle puncture. The doses used by Meyers were much smaller than those reported in cases treated by Schloss and Commiskey who reported 6 recoveries in 7 cases treated with injections of from 10 c.c. to 20 c.c. of fresh blood, a varying number of injections being used for each case. The fatal case was in an infant who had suffered from multiple hemorrhages for eight days and was in a moribund condition when treatment was begun. This patient died three and a half hours after admission to the hospital, having received only a single injection of 10 c.c. of blood.

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**The Results of Anti-typhoid Vaccination in the Army in 1911, and its Suitability for Use in Civil Communities.**—Russell (*Jour. Amer. Med. Assoc.*, 1912, lviii, 1331) gives a brief review of antityphoid vaccination from its introduction in 1896 to the present time. He believes that the lack of uniform success with the earlier inoculations was due to faulty technique in the preparation of the vaccine. The vaccine used in the United States Army inoculations is prepared by growing an avirulent strain of typhoid bacilli on agar for twenty-four hours. The resultant growth is washed off in normal saline solution, standardized by counting the bacilli, killed by heating to 55° C. for one hour and then 0.25 per cent. of tricresol is added as a matter of safety. Preliminary experiments with the vaccine prepared in this manner showed that it produced a high degree of immunity without, at the same time, causing severe general or local reactions. The vaccine is injected into the subcutaneous tissue (not into the muscles or into the skin) of the arm, at the level of the insertion of the deltoid muscle, the necessary skin sterilization having been accomplished by tincture of iodine. Three injections are given at ten day intervals—the first contains 500,000,000 bacteria, the second and third 1,000,000,000 each. As a rule, there is a local reaction consisting of a red and tender area about the size of the palm of the hand, which usually subsides within forty-eight hours. The general reaction, when present, shows itself by malaise, headache, fever, occasional chills, quite rarely by nausea, vomiting or diarrhea, and in exceptional instances by transient albuminuria. General reactions rarely appear in children and in young people and a severe reaction occurs in only one to three persons per thousand. Russell gives some very striking tables comparing the incidence of typhoid fever in the troops at Jacksonville in 1898 with those mobilized in the recent army maneuvers at San Antonio, Texas. The two divisions were encamped under nearly the same conditions although camp sanitation was probably much better in the case of the maneuver division. Of 10,759 in the Jacksonville camp there were 1,729 undoubted cases of typhoid and 964 additional cases in which the diagnosis of typhoid was probable. In all there were 248 deaths due to typhoid fever. Of 12,801 in the maneuver division, only one mild case of typhoid fever developed. Russell attributes this striking difference mainly to the fact that the men of the maneuver division had received protective inoculations of

the antityphoid vaccine. During the period of encampment of the maneuver division there were 49 cases of typhoid with 19 deaths. Among the civil population of San Antonio, and in Galveston 192 cases were reported during the same period. The men of the maneuver division frequently visited the cities of Galveston and San Antonio and thus there was frequent chance of infection. Russell believes that antityphoid vaccination is applicable in civil practice to a great extent particularly in epidemics and cites the experience learned from the Toerington, Conn., epidemic. His conclusions are as follows: (1) Antityphoid vaccination in healthy persons is a harmless procedure. (2) It confers almost absolute immunity against infection. (3) It is the principal cause of the immunity of our troops against typhoid in the recent Texas maneuvers. (4) The duration of the immunity is not yet determined, but is assuredly two and one-half years, and probably longer. (5) Only in exceptional instances does its administration cause an appreciable degree of personal discomfort. (6) It apparently protects against the chronic bacillus carrier and is, at present, the only known means by which a person can be protected against typhoid under all conditions. (7) All persons whose professions or duty involves contact with the sick should be immunized. (8) The general vaccination of an entire community is feasible and could be done without interfering with general sanitary improvements, and should be urged wherever the typhoid rate is high.

**Tincture of Digitalis—Its Potency and Keeping Properties.**—Goodall (*British Med. Jour.*, 1912, 2677, 887) has examined a number of samples of tincture of digitalis during a period of three years with special reference to their strength and stability. He found that nearly 50 per cent. of samples of digitalis made by manufacturing chemists of repute showed a departure from the average standard of potency. The limits of this variation were from 275 per cent. overstrength to 40 per cent. understrength. In other words the effect of a dose of 10 minims might be that of $37\frac{1}{2}$ minims or of 6 minims. Tincture of digitalis probably retains its full activity for one year, but after that period deterioration of its potency to an important extent is likely to take place.

## PEDIATRICS

UNDER THE CHARGE OF

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**The Treatment of Chorea Minor.**—J. Grober (*Deutsch. med. Woch.*, 1912, xxxviii, 833) places chorea minor among the acute infectious diseases, and notes the close relationship of this disease to acute articular rheumatism. The portal of entry for the specific cause is presumably the nasopharynx and tonsil, as is the case in epidemic meningitis and

anterior poliomyelitis. This indicates the importance of insisting on thorough and regular cleansing of the mouth and pharynx of the patient with antiseptic gargles and mouth washes. In chorea minor the symptoms of an acute infection are limited to the first few days in the form of moderate fever, and occasional sore throat, the fever itself needing little or no treatment. The advent of acute articular symptoms or cardiac involvement calls for special treatment. In associated articular conditions Grober has found no influence on the course of the disease from the use of salicylates or aspirin. On the contrary, these drugs in children often cause physical and mental discomfort. Psychic treatment is of the utmost importance. The absence of all exciting influences, absolute rest, of both body and mind, and isolation in severe cases, are essential. The diet should be soft or liquid, given frequently in small quantities. The knowledge and dexterity of the nurse are important in feeding the severe cases and in protecting their bodies from injury. The crib or bed should be padded on all sides to prevent the patient from injuring himself during violent choreic movements. Immersion for a long period of time in warm baths, 34° to 37°, three times a day often reduces the choreic movements, induces sleep, and increases the appetite. The effect of the baths is often accentuated by adding brine, salt or carbonic acid. The effects of bathing on the heart must be carefully watched. The treatment of chorea by the galvanic current is useless and the faradic current is harmful. Treatment by massage and gymnastic movements is ill-advised and tends to increase the general irritability. Arsenic has no logical effect on chorea except in influencing the resulting anemia which is due to diminished food intake. Fowler's solution is preferred. In the line of sedatives, Grober prefers the bromides to veronal or chloretone, and in extreme cases uses chloral hydrate. Morphine should not be used except as a last resort. The probability of cardiac involvement makes the use of the last two drugs a serious matter. Some abnormality of the heart occurs in almost every case of chorea. Slight irregularity of pulse or blood flow, albumin and casts in the urine, slight edema of the feet or lower eyelids, peripheral cyanosis and cardiac murmurs can be found and are irregular and inconstant, varying from day to day. In cardiac complication ice caps on the præcordium and immersion in warm baths are of questionable safety. Digitalis and strophanthus are indicated only when loss of compensation is threatened. Good nourishment in convalescence is important and a long period of freedom from school and removal to the country if possible is of the greatest importance in establishing a permanent cure and preventing a relapse.

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**Duration of the Infectious Period in Scarlet Fever.**—A. BAGINSKY (*Deutsch. med. Woch.*, 1912, xxxviii, 746) submits the results of an investigation into the length of time a scarlet fever case may remain infectious after it has been discharged from hospital as cured. He appends an interesting diagram of 45 "return cases" in which members of the family contracted the disease from children returned as cured. The cases were isolated in hospital for forty-two days, with a few exceptions. Of the 45 cases which carried the infection to their homes, all were apparently perfectly well except 2 suffering from an otitis.

There was no trace of desquamations left in any of the cases. Seven "return cases" spread the infection within three days of their return home. Six cases transmitted infection four days after their return. These cases were all in the hospital for forty-two days, showed no abnormality in any way when discharged and still carried infection back to their families. This shows that the regulation, six weeks isolation is not long enough. The majority of infections occurred between three and four days after the return, although a number occurred up to the seventh day. This substantiates the accepted incubation period. By the process of exclusion Baginsky concludes that in the apparently recovered cases which carry the infection the naso-pharynx is the seat of the infectious substance. Out of 12 cases of scarlet fever occurring suddenly and sporadically on the surgical wards of the hospital 6 of them occurred in cases of burns of the body surface, showing a remarkable relation between scarlet fever infection and superficial or skin burns. Probably the burned child is particularly susceptible and the contagion is present in some near-by, apparently well child. Both Baginsky and Sommerfield look to the streptococcus as one of the chief factors of this contagium of scarlet fever. No one can say exactly how long a case should remain in isolation, but it is clear that the period should be longer than the present regulation of six weeks. Baginsky suggests the establishment of stations or convalescent homes where children can be kept for a time and observed after their discharge from hospital as apparently cured.

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**Significance of the Facialis Phenomenon in Later Childhood.**—H. NEUMANN (*Deutsch. med. Woch.*, 1912, xxxviii, 813) describes the facialis phenomenon as a sudden contraction or spasm of the muscles of the nose, eye, and forehead, supplied by the facial nerve, when a sharp tap is given over a point midway between the zygomatic arch and the corner of the mouth on one side. At times fibrillary twitching around the eye and nose take the place of the combined spasm of the muscles. This phenomenon is of great value in the diagnosis of infantile tetany and in the prevention and treatment of laryngismus stridulus and allied spasms. This phenomenon is even more frequently found during early school-life than during the first years of life. The facialis phenomenon in older children is possibly the evidence of a masked infantile tetany. Not only does this phenomenon indicate a masked tetany through increased motor irritability of peripheral nerves, but it shows a relation to neuropathic conditions and has been found present in 50 per cent. to 80 per cent. in neuropathic children, aged between four and eighteen years. As this age increases the phenomenon appears less marked. Again, the condition may not develop until during adolescence and tetany and isolated facialis phenomena in late adolescence have a particular relation to hereditary neuropathy. The phenomenon is found in a large number of children with abnormal psychic and sensory irritability, as evidenced more or less by over-sensitiveness to sights and sounds, in disturbances of normal sleep, and in terrors of various kinds. The presence of the facialis phenomenon often leads to the discovery of these general symptoms. The strength of the phenomenon, however, does not indicate the grade of the neuropathy. The phenomenon is a valuable objective evidence of the neuropathic constitution.

# OBSTETRICS

UNDER THE CHARGE OF

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**The Cause of Rupture in Tubal Pregnancy.**—KIUTSI (*Archiv f. Gynäk.*, 1911, Band xciv, Heft 2,) gives the results of his extensive study of this question in Veit's clinic in Halle. His paper is fully illustrated. He characterizes such rupture as acute bursting of the capsule of the embryo. Examination of specimens show various changes in the villi, extravasation of blood, engorged veins, infiltration of blood in the connective tissue, and symptoms of engorgement. The cause he finds to be the occlusion of veins in the intervillous spaces by the growth of the villi. The arterials bring the blood into these spaces, but the pressure of the villi prevents its return by the veins. This process gradually produces a thinning in the capsule of the embryo. The edges of the opening are not usually covered by fetal cells. The trophoblast does not extend to the edge of the ruptured tissue. If fetal cells rupture the capsule they must always penetrate the maternal tissue, and in such a case would even attack the peritoneum. A growth of the villi may be described as apoplexy of the villi, as ischemia of the villi, or as a combination of the two. If the tissues are greatly compressed the apoplectic portion is usually on the periphery at the summit of the villus. The fetal erythroblasts often take the form of free nuclei. These specimens also show in the neighborhood of the principal rupture of the capsule, the giving way of intracapsular tissue by congestion, and extravasation of blood in the connective tissue. The inner layers of the capsule undergo retrogressive changes. The hemorrhage which threatens the patient's life occurs when rupture of the tissues opens the small arteries; also when the tissues surrounding these vessels are comparatively thin, and no efficient stoppage of the hemorrhage from pressure develops. The death of the embryo results from the disturbance of circulation in the villi, and is of secondary consequence to the intervillous congestion. In general, the bursting of the pregnant tube results from abnormal growth of villi, dilatation of veins, and intervillous extravasation of blood. Mechanical violence or contraction or torsion of the tube favor this. Undoubtedly previous inflammation predisposes to this accident. Observation shows that the ovum can develop in the tube without the presence of mucous membrane.

**The Prevention of the Formation of Striæ of Pregnancy.**—Those patients who object to the formation of the characteristic striæ of pregnancy, and consider them a deformity, may find comfort in BARFURTH'S success in the clinic at Rostock, in preventing this change by massage (*Zentralbl. f. Gynäk.*, 1911, No. 51). Barfurth reports 12 cases in which massage was given by student midwives. Those portions of the abdomen where striæ most often develop were treated by

stroking motions, pressure being gently exercised upon the tissue held between the thumb and finger. The abdominal skin was massaged in circular and radial motions from the umbilicus, and the tissues of the breast were similarly treated. The thighs and hips were massaged in various directions. Oil was used before the massage. In most cases daily massage of fifteen to thirty minutes sufficed, but where the skin was excessively resisting the patient received two treatments daily. Occasionally manipulation was so painful that it was abandoned. The patient improved if the skin became softer and more distensible. In the great majority of cases the treatment was agreeable to the patient.

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**Medical Education and the Midwife Problem in the United States.**—Williams (*Jour. Amer. Med. Assoc.*, January 6, 1912) sent a list of questions to the professors of obstetrics, in 120 medical schools, giving the full four-year course; 43 replied. When these replies are analyzed, they indicate that many professors are inadequately prepared for their duties, and have but little conception of the obligations of a professorship; that a considerable proportion are not competent to cope with all obstetrical emergencies; that nearly all complain that their teaching and hospital equipment are inadequate for the proper training of students; and a large proportion admit that the average practitioner through his lack of preparation for the practice of obstetrics may do his patient as much harm as the much maligned midwife. As regards what is needed to make the equipment of American medical schools competent for obstetrical training, it was found that this department was unusually inferior to others in ward accommodations, intelligent and educated assistants, and especially in broad-minded scientifically trained teachers, and properly equipped laboratories for investigating work. It is not surprising from this fact to find that one-fourth of the entire number of teachers who replied stated that they did not consider the ordinary graduate from their schools competent to practice obstetrics; while others considered the medical graduate as a fairly efficient man midwife. Williams states that in his own experience students are unfit on graduation to practise obstetrics in its broad sense, and are scarcely prepared to handle normal cases. As regards the attendance in labor cases by midwives, it is found that very few practise in Montreal and but a small number in Boston. In the greater number of large American cities they conduct from 40 to 60 per cent. of all labor cases. There is no efficient and satisfactory control of these midwives in any portion of the country. More than one-half of the teachers replying consider that general practitioners lose proportionately as many women from puerperal infection as do midwives. When the question is raised as to how this bad result is obtained, the majority believe that ill-judged and improperly performed operations, in the hands of the general practitioner, cause as many deaths as result from the mistakes of incompetent midwives. When the question of improving these conditions is raised, general improvement in medical education is a fundamental necessity. Obstetric professors must be especially trained for this work, and devote themselves largely to the care of hospital patients, the proper training of assistants and students, and the advancement of knowledge. Medical

faculties and hospitals must recognize that obstetrics is a fundamental branch of medicine, requiring a scientifically trained man as a teacher, with a broad grasp of the subject. The general practitioner must realize that he is competent to conduct only normal cases of labor, and that major obstetrics, as major surgery, should be undertaken only by especially trained men, in control of abundant hospital facilities. Applicants for license to practise should submit a statement certifying that they have seen, delivered, and personally examined, under appropriate clinical conditions, at least ten women. The public must understand that poorly trained doctors are dangerous, that most of the disorders of women result from poor obstetrics, and that poor women, in fairly well-conducted free hospitals usually receive better care than well-to-do women in their own homes; and that competent obstetricians will be forthcoming so soon as the public is willing to recognize them as such. Obstetric charities must be increased by free hospitals and out-patient service for the poor, and proper hospital accommodations for those in moderate circumstances. Visiting obstetric nurses and helpers trained to work under them, can be of service. Midwives should be gradually abolished in large cities and replaced by obstetric charities. The reviewer gladly contributed replies to the questions sent and considers the investigation most timely. He further thinks that a considerable responsibility lies upon teachers of obstetrics in the conception which they give to medical students concerning this branch of medicine. While the fundamental facts of obstetric surgery should be taught to all graduates, it is the duty of the obstetric teacher to warn the entire class that but a small proportion of them will become competent obstetric surgeons. These only should undertake difficult forceps extraction, version, placenta prævia, eclampsia, craniotomy, opening the pubic girdle, Cesarean section, ectopic gestation, separation of the placenta, and ruptured uterus. The majority of a graduating class should early determine whether or not they propose to do surgery, obstetric or other, and unless they find themselves with unusual ability and equipment they should decline obstetric surgery. Normal parturition without complications comes within the scope of the average graduate and practitioner, provided he is not in a position to infect his patient. Medical graduates and general practitioners sometimes allege that obstetrics belong to general practice. By some who cater to the general profession for consultations, obstetrics has been termed the specialty of the general practitioner. If successful general practitioners are asked whether they do obstetric work from choice or from necessity, in my experience they invariably reply that they do it only to keep the medical practice of the family. If they could do so, they would be quite willing to turn all prolonged and complicated cases of parturition over to a competent obstetrician, who in return would not interfere with the medical practice of the family. Unless one is able and equipped to do obstetric work it does not pay, and by the demands upon the time and strength of the obstetrician, it interferes most seriously with general medical work. Furthermore, the physician who must treat the exanthematous diseases of childhood, and the various contagious diseases, is not a safe or suitable person to conduct confinements. Radical improvement in this direction will not become general until the economic side

of the problem is demonstrated. When a man learns that in the long run it will cost him less to have his wife receive proper attention in labor, avoiding serious lacerations, and promptly repairing those which are inevitable, he will be willing to pay a fair price for such service. It is cheaper than a badly conducted confinement at a cheap rate and the expense of a secondary operation by a surgeon or gynecologist later. The saving of infant life through competent obstetric work does not always appeal to those who must struggle to make a living. This is, however, a question of national importance, and in other countries has received the careful attention of governments and philanthropists.

## GYNECOLOGY

UNDER THE CHARGE OF

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**Vaginal Hysterectomy Under Local Anesthesia.**—RUGE (*Zentralbl. f. Gynec.*, 1912, xxxvi, 561) believes that, while ordinary infiltration anesthesia has a great field of usefulness in gynecology as in other branches of surgery, that produced by blocking the nerve-trunks at a distance from the field of operation is preferable, since the appearance and consistency of the tissue in which the operation is to be performed is not altered. He has devised the following technique for the performance of complete vaginal hysterectomy, and other major vaginal operations. After disinfecting the vagina the long, thin needle of a "Record" syringe is introduced into the parametrial tissue to one side of the cervix to a depth of 4 to 5 cm., being directed in a somewhat lateral direction, in order to strike the nerve trunks before they have undergone their ultimate subdivisions. If the needle is introduced slowly, most vessels, and any coils of intestine with which it may come in contact, will be pushed aside and not injured. Should a vein be punctured, however, blood will begin to flow out of the neddle, which must then be drawn back a little, and advanced in a slightly different direction. When the needle has been satisfactorily introduced the 10 c.c. syringe is attached, and, gradually withdrawing the needle, the solution injected. The process is repeated on the opposite side; then at two points in the anterior and two in the posterior vaginal vault similar injections of 3 to 5 cc. of fluid are made. In the anterior vaginal vault it is necessary to introduce the needle 2 to 3 cm. deep, but in the posterior only just through the mucosa. As injection fluid Ruge uses a 1 per cent. novocain solution, to each 100 c.c. of which 5 drops of a 1 to 1000 adrenalin solution are added. It is sterilized by boiling immediately before use. The amount used is about 40 c.c., but it is practically non-toxic, and much larger amounts could be employed with impunity. The vagina is rendered anesthetic by

swabbing it out with a sponge covered with cycloform powder. To eliminate pain from pulling on the bladder, 5 c.c. of the injection fluid are introduced into it through the catheter. It is necessary to wait twenty to thirty minutes for the anesthesia to become effective, but it then lasts one and a half to two hours. Ruge reports having recently operated in this manner on two patients, neither of whom felt anything during the entire operation, not even the introduction of large gauze pads to hold back the intestines, nor seizing the parietal peritoneum with toothed forceps. No morphine, scopolamine, or other narcotics were given. Ruge considers this method just as satisfactory as lumbar anesthesia, and far less dangerous.

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**Lymphatics of the Clitoris.**—Rouviére (*Ann. de Gyn. et d'Obstet.*, 1912, xxxix, 273) has been struck by the fact that at times, following extirpation of the clitoris for carcinoma, recurrence takes place in the small pelvis directly, without involvement of the inguinal or retrocrural glands, an occurrence which should be impossible if the classical description of the anatomy of the lymphatics of this region is correct. He has therefore undertaken some investigations into the lymphatic supply of the clitoris, and has been able to demonstrate by injection methods the occasional occurrence of lymph vessels which establish a direct connection between that organ and the hypogastric glands in the pelvis—a finding similar to that of Küttner with regard to the penis. He was not able to find these direct lymph channels in all cases, this being due, he thinks, rather to an irregularity in their occurrence than to any fault in technique. He considers, however, that the demonstration that they do occur in a certain number of cases explains, in part at least, the extremely unfavorable prognosis that it usually associated with carcinoma about the clitoris, since in such subjects it is almost impossible to excise thoroughly the entire tributary area.

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**Composition of the Menstrual Fluid.**—The results of careful chemical analyses of the fluid obtained from 10 cases of hematocolpos due to atresia are reported by Bell (*Jour. Obst. and Gyn., Brit. Emp.*, 1912, xxi, 209). Urea was never found; mucin, on the other hand, was always present in large amount, arising from the cervix and vagina. Blood, estimated from the amount of iron present, formed on an average somewhat less than 50 per cent. of the fluid. Fibrinogen and fibrin-ferment were always absent; to this fact is due, Bell believes, the non-coagulability of menstrual fluid, and not to the presence of mucin or of lactic acid, as has frequently been taught. He believes that this lack of fibrinogen and fibrin-ferment in the menstrual fluid is the result of some vital function of the healthy endometrium, which destroys or extracts it, since there is nothing in the uterine or vaginal secretions to destroy the fibrin-ferment, or to prevent clotting of the blood if it were present. This Bell has shown by adding to normal sodium fluoride solution an equal quantity of hematocolpos fluid, together with fibrin-ferment, obtaining a good clot within ten minutes. In all the specimens examined lactic acid was found, although all were sterile but two, in which there were some colon bacilli, probably due to contamination during or after removal. In no case were Döderlein's bacilli found. Bell concludes, therefore, that the acidity of the vagina is not due to

this bacillus, but to the lactic acid, which is formed by the action of some cellular enzyme on the mucin present. The calcium content of the hematocolpos fluid was invariably found to be high, amounting in some cases to six times or more that of normal blood.

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**Arsenic as a Factor in Menstruation.**—Some rather interesting, even though as yet not entirely conclusive investigations into the arsenic-storing function of the uterine glands have been carried out by IMCHANITZKY-RIES and J. RIES (*Münch. med. Woch.*, 1912, lix, 1084). These authors have demonstrated, by means of the Marsh and Gutzeit tests, the presence of small quantities of arsenic in the endometrium during menstruation. In the post-menstrual stage arsenic is entirely lacking, to reappear later in the interval, being present in the largest amount just before the onset of menstruation. In the endometrium of a woman, aged sixty-five years, they were unable to find any traces of arsenic. The theory of the investigators is that arsenic, a considerable quantity of which is taken in with the daily food, is stored up in the uterine glands, and is given off in the mucoid secretion which is eliminated by them during the pre-menstrual stage, but which remains blocked up in the tortuous glands until it is discharged during menstruation. That menstrual fluid does actually contain arsenic has been demonstrated by Gautier, who found that about 0.15 mg. is given off in this way on an average at each menstrual period. It has been frequently demonstrated that arsenic given therapeutically to men can be recovered in the urine; in women, however, this is not the case, a futher confirmation, the authors believe, of their theory that it is stored in the uterine glands. They have found that a much larger quanitty of arsenic is always present in the tissues of fetuses and newly-born animals than in those of adults; it apparently has the same importance for the growth of the fetus as does, for instance, phosphorus. They believe that during childhood, while active growth is going on, the arsenic received from the mother, and that later taken in with the food, is utilized in body-building. At puberty, however, an excess of arsenic begins to accumulate; the uterine glands begin to functionate, and to store up this excess, until a sufficient concentration is reached for it to act as a poison. The entire endometrium is affected, the ordinary histologic picture of arsenic poisoning being produced—desquamation of epithelium, fatty degeneration, transudation paralysis of vessel walls, with dilatation of the vessels and escape of blood. In order to determine if the presence of arsenic in the endometrium would have any inhibiting effect on impregnation, the authors investigated the action of living spermatozoa when brought in contact with arsenic solutions on the warm stage of the microscope. They found to their astonishment that such solutions up to 1 per cent. strength (much stronger than is ever present in the endometrium) not only do not have any deleterious action on spermatozoa, but rather seem to increase their activity. In conclusion, the authors state that they consider their experiments so far as suggestive rather than conclusive, and that they merely wish to indicate that this arsenic-storing function of the uterine glands may be one of the numerous factors concerned in the production of the complex phenomenon of menstruation.

# DERMATOLOGY

UNDER THE CHARGE OF

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**A Cryptogamic Parasite Found in a Dermatosis of the Type of Pityriasis Rosea.**—Du Bois (*Annales de Dermatologie et de Syphiligraphie*, 1912, No. 1) reports the finding of a cryptogamic parasite in three cases of a cutaneous disease, one of which was of the type of the pityriasis rosea of Gibert, and the other two resemble varieties of this affection. The parasite consisted of spores of variable size grouped in clusters, without mycelia, in the orifices of the follicles. It did not grow in any of the ordinary media, and was not inoculable. In several of its characters it resembled the microsporon described by Vidal as the cause of pityriasis circinata. Du Bois believes further research will demonstrate its presence in all cases of pityriasis rosea, of which it is the probable cause. He proposes to name it "microsporon dispar."

**Bullous Antipyrine Eruptions of the Buccal Cavity.**—Nicolas and Moutot (*Annales de Dermatologie et de Syphiligraphie*, 1911, No. 11), reporting a case of bullous eruption in the buccal cavity due to the ingestion of antipyrine, especially call attention to the possibility of such eruptions being limited exclusively to this region, and to the difficulties which may surround the diagnosis under such circumstances. The first symptoms, which may appear within a few minutes after the ingestion of the drug, but usually not until from three to six hours have elapsed, are a bright carmine redness of the mucous membrane, with more or less swelling, pain, and abundant salivation. After a period varying from a half-hour to two or three days, bullæ appear which rupture after a time, leaving a superficial lesion. Owing to the pain which accompanies the eruption movements of the tongue and jaws are difficult, and there is more or less dysphagia. Although, as a rule, there are no general symptoms, moderate elevation of temperature, dyspnea, vertigo, and vomiting have been observed in some cases.

**Skin Changes in Leukemias.**—H. H. Hazen (*Jour. Cutan. Dis.*, October, 1911) refers to the group of lymphomata involving the skin (which includes leukemia and pseudo-leukemia, lymphosarcomatosis, lymphodermia perniciosa, mycosis fungoides, and chloroma and myeloma). Mycosis fungoides is an aleukemic lymphomatosis and may become leukemia. Reference is made to the "serum reaction" lately discovered by Joltrain and Brin and described by de Beourmann and Verdun which may possibly clear up the relationship. Hazen thinks that the skin lesions of leukemia may probably be compared with the nodules of internal organs met with in splenomyelogenous leukemia.

**Bullous Eruption Associated with Appendix Abscess.**—J. H. SEQUEIRA (*Brit. Jour. of Derm.*, September, 1911) reports the case of a boy, aged three years, who showed numerous blebs on upper and lower extremities, the attack lasting a week, the blebs drying up. A second similar attack, and again a third attack occurred. The lesions suggested a beginning dermatitis herpetiformis. The child was now suddenly taken ill with abdominal pain, and within twenty-four hours was operated upon and a gangrenous perforated appendix found. The blebs on the skin disappeared in a week without any treatment.

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**Treatment of Acne by Vaccines.**—MORRIS AND DORE (*Brit. Jour. of Derm.*, October, 1911) quoting Engman's experience and method state that from their own observations they were not able to agree with Engman in regarding "acne bacillus vaccine as one of the most brilliant therapeutic agents in dermatology, comparable in its effects to that of antitoxin on the diphtheritic membrane." They were not able to claim more for the vaccine therapy in acne than that it is a useful adjuvant of the ordinary forms of treatment. There was no evidence that it was capable of inducing true immunity.

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**Seven Hundred Consecutive Cases of Tinea Capitis.** —H. M. SCOTT, of London (*Brit. Jour. of Derm.*, October, 1911), states that these cases were seen at the London Hospital, 405 being boys and 295 girls. Of the 700 cases (all examined by the microscope and the fungus demonstrated) 628 were examples of microsporon ringworm and 72 were of endothrix ringworm. The most common ages were from the sixth to the eighth years. The treatment was by the Röntgen rays, the written consent of the parents being first obtained. As a routine measure the whole scalp was treated, five-exposure method of Kienbock as modified by Adamson being employed. Out of 3000 cases of tinea capitis treated at the Hospital no single instance of permanent alopecia occurred.

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**Treatment of Erysipelas.**—T. PONTANO (*Policlinico, Rome*, No. 1, 1912) states that in two and one-half years in the Polyclinic, over 1000 cases of this disease were treated, 87 of whom died, but in only 47 cases was erysipelas responsible. The mortality from erysipelas is about 8 per cent. and chiefly in aged or debilitated persons. The various well-known measures for the treatment seem to have been of little value. Hot compresses of physiological salt solution, frequently renewed, reduced the heat and pain as much as the remedies tried, but did not affect the course of the disease.

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**A Case of Phenol (Carbolic Acid) Gangrene.**—F. BUCKMINSTER (*Jour. Amer. Med. Assoc.*, January 13, 1912) reports a case of an elderly man, who for a slight bruise and abrasion due to a railway accident, applied an ordinary phenolized petrolatum. After a few applications the tissues broke down into a progressively enlarging gangrenous ulcer, the lesion being upon the leg two inches below the patella. It was cleaned out and treated with hydrogen peroxide and tincture of iodine; healed but again broke down, and now indicated malignancy. At the end of several months' treatment, *x*-ray applications finally caused healing.

# PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**The Formation of Pigment.**—SCHULTZ (*Jour. of Med. Research*, April, 1912, xxvi, No. 1) publishes an interesting study of pigment formation by the dermal chromatophores, from a case of mycosis fungoides, in which the inflammatory process, of low grade, had given origin to a large number of new chromatophores in the subepidermal tissues. Thanks to these, the process of pigment formation could be studied in all its phases. As to the origin of the chromatophore, Schultz considers that no doubt can exist of its mesoblastic origin, to which most readers will agree. He finds this difference between the chromatophores and other mesodermal connective tissue cells, that the former are never seen to form fibrils, and that this is not fortuitous but indicates that the formation of pigment is a special function undertaken by the cell, which thus is freed from the necessity of performing the function of fibril formation. Schultz considers that the pigment is not derived from hemoglobin, nor from the cytoplasm alone, nor is it a degeneration in the ordinary sense of the word; rather it is a definite extension of chromatin from the nucleus into the cytoplasm, and this chromatin takes the staining reactions of nuclear substance, and becomes transformed into pigment; in this transformation of the extruded chromatin into pigment, Schultz thinks the cytoplasm plays a part, either by chemical or catalytic action; and he thus considers that the pigment is a product of nuclear material, and that this nuclear material must not be considered to be cast off as the result of a degenerative process. Those appearances in chromatophores which might be cited as implying degeneration, such as a partite nucleus, Schultz considers to be merely the signs of senescence in a cell that has fulfilled its life-purpose in the usual way.

**Experimental Measles in Monkeys.**—LUCAS and PRIZER (*Jour. of Med. Research*, April, 1912, xxvi, No. 1) have succeeded in producing measles in monkeys by the inoculation, intracerebrally and intraperitoneally, of blood serum from a patient thirty-six hours after the initial rise of temperature and six hours before the appearance of the rash. The inoculated monkeys, after a definite incubation period of six days in one case, showed systemic signs, and on the tenth day Koplik spots could be recognized (this for the first time); during the acute stage of the disease erythema of the face and forehead were noticed, but no more characteristic rash. During the preëruptive period a leukopenia was demonstrated which involved polymorphonuclears, lymphocytes and large mononuclears.

**A New Anaerobic Bacillus in Typhoid Stools.**—Loris Melikov (*Compt. Rend. de la Soc. de Biol.*, 1911, lxx, No. 19) publishes his results from growing typhoid fecal matter in liquid medium made of bile, bouillon, and white of egg. From this, at the end of two or three days, subcultures in glucose are made and fine transparent colonies, appear which consist of short bacilli with rounded ends, becoming longer and bent, even curved in older cultures, gram-positive, and non-motile. They grow only at 37° C. and anaërobically, and are proteolytic. The organism is virulent for guinea-pigs, but loses virulence rapidly. Animals dead 12 to 24 hours after inoculation show tumefaction and ulceration of the lymph follicles and Peyer's patches. The organism has not yet been found in stools from other than typhoid patients, and gives positive agglutination with the serum of those suffering from typhoid. It may be that this is the actual agent in the production of typhoid fever.

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**Pneumococcus Influenza.**—The statement that there is no influenza without the influenza bacillus is again denied by C. Leede (*Zeits. f. Hyg. u. Infektionskrankh.*, 1912, Band lxxi, Heft 3), who produces a series of cases to that end. Four years ago Curschmann published 77 cases from 49 of which the influenza bacillus was not obtained, while the pneumococcus was present in so great numbers that he considered it the causative agent. Observer after observer came forward with cases whose contagiousness, apart from their clinical symptoms, spoke for the diagnosis of influenza, yet whose bacteriological examinations showed pneumococcus to be the prevailing germ. Not that pneumococcus was the only organism, for in some cases, not pneumococcus, but streptococcus and staphylococcus were found, and sometimes combinations of these. There are cases that resemble typhoid fever, whose respiratory signs and onset are indicative of influenza, yet whose blood cultures show pneumococcus. In fine, Leede brings forward more cases to show that influenza, as known to the practitioner is a symptom complex. that may be excited by different bacteria, rather than a specific disease due only to the influenza bacillus. Of these different bacteria, the pneumococcus is the most important, and it is able to set up different degrees of sudden infection, now true pneumonia, now a typhoid-like attack, now a short febrile attack, often designated influenza. Leede futher points out that the pneumococcus may attack the bowel giving a colitis at times ulcerative, like that known in true influenza.

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**The Detection of Horse Flesh in Sausages.**—For long enough the comic papers have depicted the sausages proclaiming their origin by moving up on the platter to fill the gap made by removal of the first of the row: this homely viand gains one step in the direction of becoming articulate by the work of G. Seiffert (*Zeits. f. Hyg. u. Infektionskrankh.*, 1912, Band xxxi, Heft 3), who points out the accuracy of the fixation of complement test in the detection of adulteration of sausages by horseflesh. He uses rabbit-serum, of which $\frac{1}{10}$ c.c. gives a reaction with horse serum in a dilution of 1 in 20,000 within one minute. The test is accurate for raw, cooked, and smoked horseflesh as well as that treated by ether and antiformin in most minute quantities, while controls with beef and human serum remain negative.

**The Local Effect of Orchitis in Mumps.**—So rarely is pathological effect of mumps upon the testis to be observed post mortem that it is interesting to note that HALL (*Virchow's Archiv.*, 1912, Band ccvii), obtained a case in a youth, aged eighteen years, who had suffered from mumps and orchitis a year before his death. There was visible atrophy of the testis; microscopically, there was definite atrophy of the tubules, with a diffuse fibrosis.

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**Trichiniasis.**—M. ROMANOVITCH (*Ann. de l'Inst. Pasteur*, May 25, 1912, xxvi, No. 5), although for reasons given adhering to the old nomenclature, points out that in future, following Raillet, we should call the trichina the *Trichinella* spiralis. The female penetrates the mucosa of the bowel, but does not pass the muscularis mucosæ; it deposits its larvæ in or close to lymphatic vessels, whence they are carried to the blood stream; considering this, Romanovitch thinks that where suspected meat has been eaten, it would be possible by a daily examination of the blood, to recognize the spread of the infection. Karyokinetic figures are seen frequently in the immediate neighborhood of the invaded lymphatics. The larvæ perish rapidly in the serous cavities; the muscle is, of course, its place of choice. Romanovitch points out that in traversing the intestinal mucosa, the trichina deposits as it goes the bacteria with which its surface is covered, whence arise the polymicrobic secondary infections which occur in cases infected by the worm. He appears scarcely willing to say that fever, abscess-formation, and septicemia are due to infections arising in this way, but thinks it would be hard to prove the contrary assertion. The serum of infected rats and guinea-pigs becomes toxic, as does the urine of highly infected animals; in ordinary infections, this toxicity may appear as early as the ninth day and may last a month; it is iso- and hetero-toxic. The search for specifiic autibodies in the serum has not succeeded, either in the direction of precipitins or fixation of complement. As antigen Romanovitch employed aqueous extract of measly muscle. As had been noted of others, definite reinfection was found to occur, so that it seems quite impossible to immunize animals against the parasite. Finally, no treatment, preventive or abortive, has yet been found. Salvarsan does not appear to exert any action whatever upon the larvæ. Atoxyl proved similarly inefficacious.

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